Selective Inhibition of ICAM-1 and E-Selectin Expression in Human Endothelial Cells. 2. Aryl Modifications of 4-(Aryloxy)thieno[2,3-*c*]pyridines with Fine-Tuning at C-2 Carbamides

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The elevated expression of cell adhesion molecules (CAMs) on the lumenal surface of vascular endothelial cells is a critical early event in the complex inflammatory process. The adhesive interactions of these CAMs that include E-selectin, ICAM-1, and VCAM-1 with their counter-receptors on leukocytes, such as integrins of the $\alpha_L\beta_2$ family, result in migration of the leukocytes to the site of inflammation and cause tissue injury. Pharmaceutical agents that could suppress the induced expression of one or more of these cell adhesion molecules would provide a novel mechanism to attenuate the inflammatory responses associated with chronic inflammatory diseases. A-205804 (**1**), a potent and selective inhibitor of the induced expression of E-selectin and ICAM-1 over VCAM-1, was further modified with emphasis at the C-4 and C-2 positions to identify a more potent drug candidate with a good pharmacokinetic profile and physical properties. Replacement of the C-4 sulfur linkage in **1** with an oxygen atom eliminated one of the two major metabolites for this lead molecule. The *para*-position of the 4-phenoxy group of the thieno[2,3-*c*]pyridine lead is found to be very critical for a higher in vitro potency and selectivity of E-selectin and ICAM-1 over VCAM-1 expression. This position is presumably close to the solvent-accessible region of the target protein−inhibitor complex. An attempt to install a water-solubilizing group at the *para*-position of the phenoxy group to increase the aqueous solubility of this lead series through various linkages failed to provide an ideal inhibitor. Only small substituents such as fluorine are tolerated at the *meta*- and *ortho*-positions of the 4-phenoxy to retain a good in vitro potency. Bromo, trifluoromethyl, pyrazol-1-yl, and imidazol-1-yl are among the better substituents at the *para*-position. With fine-tuning at the C-2 position we discovered a series of very potent (IC_{50} < 5 nM for ICAM-1) and selective (>200-fold vs VCAM-1) inhibitors with a good pharmacokinetic profile. Demonstrated efficacy in a rat rheumatoid arthritis model and in a mice asthma model with selected compounds is also reported.

Introduction

Cell adhesion plays a critical role in a wide array of biological processes including hemostasis, immune response, inflammation, and embryogenesis.[1] The cell adhesion molecules (CAMs) are a group of cell-surface proteins that are involved in mediating adhesion of cells to each other and of cells to the extracellular matrix. The interaction of the adhesion molecules on vascular endothelial cells (e.g., E-selectin, ICAM-1, and VCAM-1) with their counter-receptors on circulating leukocytes (e.g., Lewis-X antigens, β_1 and β_2 integrins) results in the capture, rolling, and firm adhesion of the leukocytes to the vascular endothelium.[2] The arrested leukocytes then transmigrate the vascular wall and move toward the lesion along the chemotactic gradient.[3,4]

The loss of adhesive interaction as well as a stimulation of adhesion may result in disease states.[5] For example, continuous recruitment of leukocytes from blood vessels into inflamed tissues perpetuates tissue injury in chronic inflammation.[6] An early and critical step in the stimulated leukocyte recruitment is the induced expression of cell adhesion molecules on the lumenal surface of vascular endothelial cells.[7,8] Pharmaceutical agents that suppress the induced expression of one or more of these cell adhesion molecules would provide a novel mechanism to attenuate inflammatory responses.[9] An ICAM-1 antisense oligonucleotide from Isis Pharmaceuticals (ISIS 2302) has been tested in human clinical trials for several inflammatory diseases, and showed beneficial effects in early studies.[10−12] Workers at Parke-Davis reported a series of small molecules that inhibited the expression of adhesion molecules on human endothelial cells.[13,14] A series of dual inhibitors of NF-κB and activator protein 1 (AP-1) transcription factor activation have been disclosed by workers at Signal Pharmaceuticals.[15] Cell adhesion

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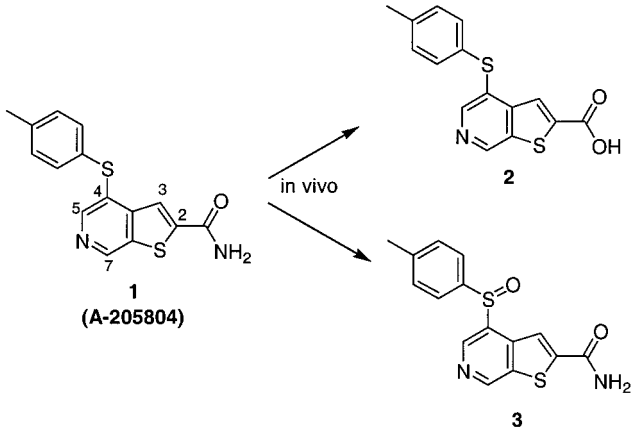
Scheme 1



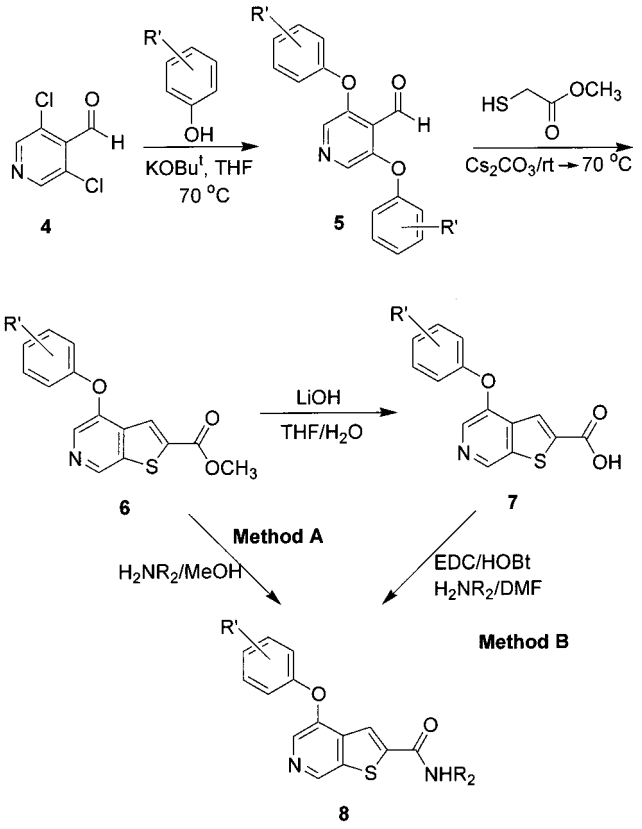
inhibitors containing dilazep as the active ingredient to VCAM-1 expression showed antiallergic, antiasthmatic, and antirheumatic activities.[16] In our previous paper, we described the identification of a potent and selective lead inhibitor of tumor necrosis factor-α (TNFα) induced E-selectin and ICAM-1 expression, namely, A-205804 (**1**) (IC_{50} = 25 nM vs ICAM-1 expression).[17] Further structure−activity relationship studies revealed that the thieno[2,3-*c*]pyridine is an optimal core structure of this lead series (Scheme 1). Preliminary biological characterization of this class of inhibitors indicated that the compounds were effective regardless of the method of activation of the endothelial cells, they were not general inhibitors of protein synthesis or gene transcription, and they had little effect on T-cell function. The lead compound **1** was an effective inhibitor of cell−cell adhesion in an in vitro flow experiment, demonstrating relevance in a model physiological system. Initial pharmacokinetic evaluation of **1** was, however, disappointing, with a low drug concentration in plasma following oral dosing in rats (5 mg/kg). Two major metabolites were identified, the products of amide hydrolysis (**2**) and sulfide oxidation (**3**) (Scheme 1).

We envisioned that replacement of the C-4 sulfur linker with an oxygen atom would address the sulfide oxidation issue. Modification of the C-2 carboxamide may reduce the potential amide cleavage in vivo. In this paper, we report that modifications of the 4-aryloxy moiety with fine-tuning at the C-2 carboxamide result in a series of highly potent, selective, and orally bioavailable inhibitors against TNFα-induced E-selectin and ICAM-1 expression. Demonstrated efficacy of these compounds in a rat rheumatoid arthritis model and in a mouse asthma model is also disclosed.

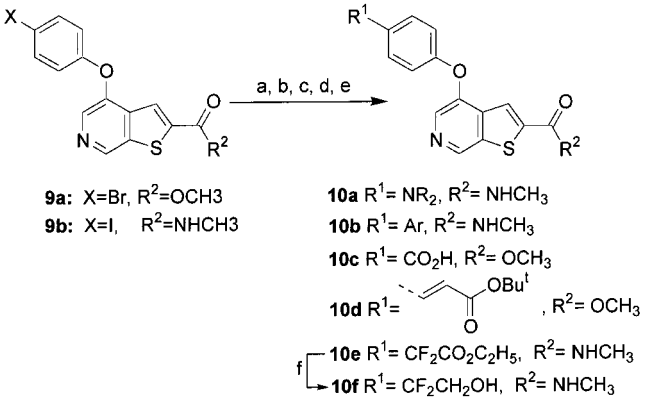
Synthetic Chemistry

Depicted in Scheme 2 is a general synthesis of 4-(aryloxy)thieno[2,3-*c*]pyridinecarboxamides. Nucleophilic displacement of both chlorides in 3,5-dichloropyridinecarboxaldehyde (**4**), which is readily available from 3,5-dichloropyridine,[17] with 2 equiv of potassium phenoxide proceeded smoothly at 70 °C to yield bis(aryl ether) **5**. Intermediate **5** was generally not purified, but rather was immediately treated with methyl thioglycolate at room temperature and/or heated to 70 °C to form thieno[2,3-*c*]pyridine ester **6**. Amidation of the ester **6** can be readily performed by the standard two-step

Scheme 2



Scheme 3[a]

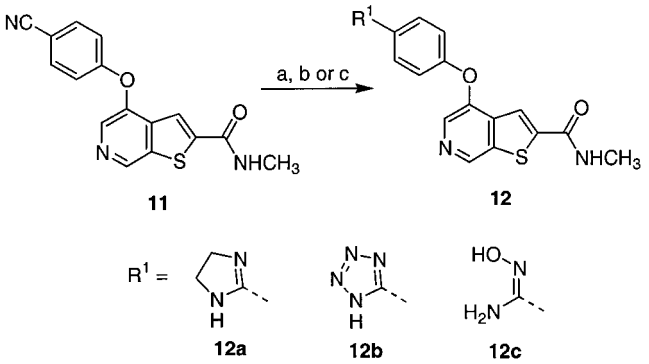


[a] Conditions: (a) $Pd_2(dba)_3$/(−)-BINAP/THF, (b) $Pd_2(dba)_3$/(*o*-tol)$_3$P/Et_3N, (c) CO/$PdCl_2$(dppf)/Et_3N/THF/H_2O, (d) *tert*-butyl acrylate/$Pd_2(dba)_3$/(*o*-tol)$_3$P/Et_3N, (e) Cu/ICF_2CO_2Et/DMSO, (f) $NaBH_4$/MeOH.

protocol, namely, hydrolysis to acid **7** followed by EDC amide coupling [EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, method B]. Heating of **6** in a methanolic solution of the desired amines also afforded the amides **8** (method A).

The *p*-amino substituents on the 4-aryloxy group of compound **10a** were installed by the Buchwald amination protocol (Scheme 3).[18] Iodide **9b**, which was prepared by the standard method depicted in Scheme 2, was heated with amines and NaOBu^t in THF in the presence of catalytic tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and (−)-BINAP to give **10a** in modest yields. The Stille-type coupling of the iodide **9b** proceeded smoothly with aryltributyltin in the presence of $Pd_2(dba)_3$ and tri(*o*-tolyl)phosphine [(*o*-Tol)$_3$P] to

Scheme 4[a]



[a] Conditions: (a) HCl/MeOH/Et_2O/ethylenediamine, (b) NaN_3/Et_3NHCl/NMP, (c) $HONH_2$·HCl/Et_3N/DMF/EtOH.

afford **10b**. Carbonylation of **9a** in a mixture of THF and H_2O with $PdCl_2(dppf)$·CH_2Cl_2 as catalyst provided the corresponding carboxylic acid **10c**. A moderately high pressure of CO (>400 psi) was required for a modest yield (30−50%). The Heck reaction of **9a** with *tert*-butyl acrylate under standard conditions yielded the cinnamide **10d**. In a method analogous to that of Kobayashi,[19] **9b** was reacted with freshly prepared copper(0) and methyl iododifluoroacetate in DMSO to give difluoroacetate **10e,** which was further reduced to alcohol **10f**.

Scheme 4 illustrates the coversion of the *p*-cyano group in compound **11** into the corresponding dihydroimidazole **12a**, tetrazole **12b**, and hydroxyamide **12c**. After a solution of nitrile **11** in a mixture of methanol and ether was saturated with HCl gas, evaporation of the volatiles gave a while solid which on exposure to ethylenediamine in refluxing methanol provided **12a**.[20] Treatment of nitrile **11** with sodium azide and catalytic triethylammonium chloride in NMP afforded tetrazole **12b**.[21] The addition of hydroxylamine to **11** in a mixture of DMF and ethanol proceeded smoothly at room temperature, giving *N*-hydroxyamidine **12c** in 68% yield.

Structure−Activity Relationship Discussion

As has been described in our previous report,[17] A-205804 (**1**) was discovered from a high-throughput screening of the Abbott compound collection followed by traditional medicinal chemistry efforts using a whole-cell functional assay. We assumed that all inhibitors are selectively targeting the same signaling pathways leading to activation of adhesion molecule expression. Since the target protein was not identified, we continued to utilize a whole-cell ELISA assay for the subsequent routine SAR studies.

As shown in Table 1, both metabolites acid **2** and sulfoxide **3** from the initial pharmacokinetic evaluation of our lead molecule **1** were inactive on inhibiting the expression of all three CAMs at the highest concentration we examined (4 μM). To remove the metabolically labile functionality, the biaryl sulfide linkage in **1** was replaced with biaryl ether (X = O). We were gratified that the resulting 4-(aryloxy)thieno[2,3-*c*]pyridine **14** presented a similar spectrum of activity against adhesion molecule expression. To eliminate the potential metabolism through benzylic oxidation, we next replaced the *p*-tolyl group of **1** with *p*-chlorophenyl. Previous studies showed that the *p*-chlorophenyl compound in the sulfide series (**13**) is equipotent with **1** against both ICAM-1 and E-selectin expression. The potency of the 4-chlorophenoxy compound **15** increased 3-fold to a respectable IC_{50} of 6 nM against E-selectin expression. As expected, **15** was more metabolically stable than **1**. Its half-life in rats increased to 2.0 h versus 15 min for compound **1** (10 mg/kg). The area under the curve (AUC_{0-8h}) for **15** increased 10 times to 1.26 μg/mL. Together with an 85% relative oral bioavailability, **15** served as a benchmark for further structural modifications of this lead series and SAR studies.

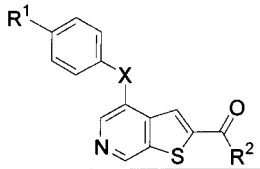
Encouraged by this initial success, we then turned our attention to the problem of amide hydrolysis. In an effort to suppress the rate of hydrolysis, the primary amide in **15** was replaced with methyl amide (**16**), ethyl amide (**17**), dimethyl amide (**18**) and 2-hydroxyethyl amide (**19**, **20**). The methyl amide **16** was nearly as potent as primary amide **15** against both E-selectin and ICAM-1 expression, while dimethyl amide **18** and 2-hydroxyethyl amide **19** were less potent compared to the corresponding primary amide (20- and 40-fold, respectively). The *p*-bromophenyl analogue **20** showed marginally improved potency versus chloride **19**. No in vitro cellular toxicity was observed at the highest concentration we tested (100 μM).

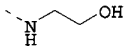
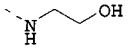
We next investigated a small set of substituents on the 4-aryloxy group to determine the optimal substitution pattern. As shown in Table 2, *meta*-substituents gave rise to 20−100-fold less potent inhibitors relative to **15**. Addition of a methyl group (**25**) at the *meta*-position of the aryloxy group of **15** reduced its affinity by 10-fold. A fluoro group was the only substituent we screened that was tolerated at this position as exemplified by **27**. The 3,5-dimethylphenoxy analogue **28** was inactive at 1 μM. All functionalities we incorporated at the *ortho*-position of the 4-aryloxy group [CH_3 (**29**), Br (**30**), allyl (**31**), and 2,3-dihydroxypropyl (**32**)] led to a dramatic loss of their potencies against CAM expression.

On the basis of these results, we concentrated our efforts on the *para*-substituted phenyl ethers. Table 3 shows the in vitro potencies and cellular toxicities of a series of such inhibitors of CAM expression with an emphasis on exploring steric and electronic effects of the *para*-substituents of the aryloxy group. A comparison of compounds **33**, **14**, **34**, **35**, **36**, and **37** on their inhibition of CAM expression versus their *para*-substituent's size [$(CH_3)_3C$ > $(CH_3)_2CH$ > C_2H_5 > CH_2 = CH > CH_3 > H] suggested that the steric size at the *para*-position was critical. The vinyl group appeared to be particularly favored with IC_{50} = 1 nM vs E-selectin. Among the four halides (**39**, **15**, **40**, and **41**) we examined, the bromo compound **40** was the most potent, and was not toxic to endothelial cells in vitro at 100 μM. The more electron-withdrawing trifluoromethyl (**42**) and cyano (**43**) groups were among the better substituents at this position. The *N*-methyl amides **44** and **45** were very potent and selective inhibitors with IC_{50} = 7 and 0.7 nM vs E-selectin, respectively.

Electron-donating substituents at the *para*-position of the 4-aryloxy groups were found to have a negative impact. Introduction of a methoxy group as exemplified in **46** disfavored inhibition of CAM expression by 8-fold versus the corresponding methyl-substituted analogue

Table 1. In Vitro Potencies and Cellular Toxicities of 4-Substituted Thieno[2,3-*c*]pyridine-2-carboxamides: Effect of the C4-Linking Group and Amide Substituent



Compound	R^1	X	R^2	CAM ELISA IC_{50} ± sem,[a] nM			Toxicity IC_{50} ± sem,[a] μM
				E-Selectin	ICAM-1	VCAM-1	(HUVEC, MTS)
1	CH_3	S	NH_2	20 ± 10	25 ± 10	>1000	152
2	CH_3	S	OH	>4000	>4000	>4000	nd[b]
13	Cl	S	NH_2	12 ± 2	48 ± 19	>4000	>100
3	CH_3	S=O	NH_2	>4000	>4000	>4000	nd
14	CH_3	O	NH_2	20 ± 10	20 ± 10	11000 ± 2600	91±1.9
15	Cl	O	NH_2	6 ± 0.5	9 ± 1.4	3900 ± 100	55 ± 0
16	Cl	O	$NHCH_3$	8 ± 0.5	17 ± 10	>1000	nd
17	Cl	O	$NHCH_2CH_3$	31 ± 3	34 ± 3	>1000	>20
18	Cl	O	$N(CH_3)_2$	100 ± 30	180 ± 70	130	nd
19	Cl	O		210 ± 5	340 ± 140	880 ± 20	nd
20	Br	O		120 ± 11	75 ± 14	>1000	>100

[a] Values for triplicate assay. SEM for multiple triplicate determinations. [b] Value not determined.

14. Incorporation of the less electron-donating but sterically similar trifluoromethoxy group in **47** led to an inhibitor which was 3 times more potent than the *p*-methoxy analogue **46**. Acetyl (**48**), ethylcarboxy (**49**), amino (**50**), and *N*-hydroxyamidine (**12c**) were comparable with a methyl substituent at this position in terms of in vitro potencies against E-selectin and ICAM-1 expression. Acetamide **51** was 20-fold less potent than amine **50**. Other substituted amino groups such as morpholine (**52**), *N*-methylpiperazine (**53**), and [3-(*N*-methylpiperazin-1-yl)propyl]amino (**54**) also were less potent inhibitors. Interestingly, when the substituent was an aromatic heterocycle such as imidazole (**55** and **56**) or pyrazole (**57**), very potent inhibition against the expression of all three CAMs was found. *N*-Triazole analogue **58** was an exception, with an IC_{50} 20 times less potent than the corresponding imidazole and pyrazole analogues. The 2-tetrazole derivative **12b** was inactive, perhaps due to its ionic nature, which may interfere with cellular penetration. Other more polar carbon-linked heterocyclic substituents such as 4,5-dihydro-2-imidazolyl (**12a**) and 1-methyl-4-imidazolyl (**59**) resulted in less potent inhibitors. Introduction of a 5-trifluoromethyl-3-oxodiazolyl (**60**) retained good in vitro potency. *p*-Phenyl, thiophen-2-yl, and furan-2-yl analogues **63**, **64**, and **65** were all very potent against both E-selectin and ICAM-1. However, their selectivity over VCAM-1 varied, with **63** being very selective while **61** and **62** were nonselective. A self-Aldol condensation of **48** led to a very interesting dimeric compound (**64**) that was surprisingly very potent and selective (IC_{50} = 2.8 nM vs E-selectin). Although there was no general rule that covered the SAR data summarized in Table 3, the potency of the dimeric **64**, along with other analogues with large *para*-substituents (e.g., **65**), suggested that the *para*-position of the 4-aryloxy group is in the region of solvent accessibility. We felt that this site may accommodate a large group which could confer desirable physicochemical properties.

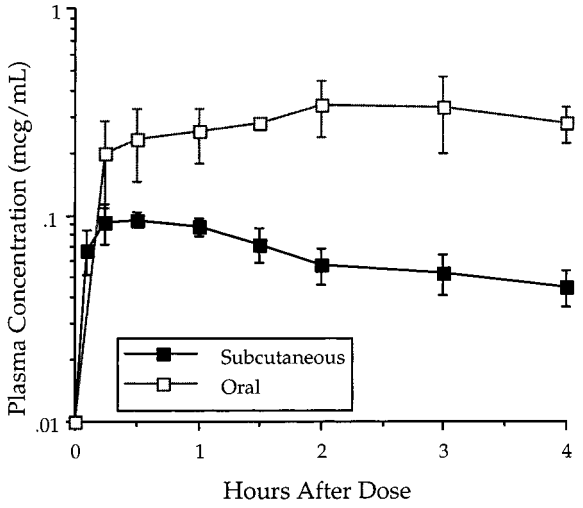
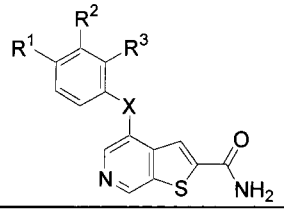
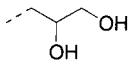


Figure 1. Pharmacokinetics of **40** (oral dose 5 mg/kg). Aqueous insolubility leads to a long half-life.

The pharmacokinetic behavior of compound **40** in rats is shown in Figure 1. The poor aqueous solubility of 0.3 μg/mL (pH 7.4, 0.05 M NaH_2PO_4 buffer) precluded intravenous administration; hence, the compound was dosed orally and subcutaneously at 5 mg/kg. Figure 1 shows the drug concentration of **40** in plasma as a function of time (8 h time course). No major metabolite was detected by HPLC analysis of the plasma sample, clearly indicating that replacement of sulfur with oxygen was beneficial. The long half-life is perhaps the result of slow dissolution, leading to sustained release from the GI track. In an effort to increase the aqueous solubility to allow intravenous administration, we tried to install a water-solubilizing group into our lead inhibitor in the region of solvent accessibility. Since the 4-vinyl analogue **34** was among the most potent inhibi-

Table 2. In Vitro Potencies and Cellular Toxicities of 4-(Aryloxy)thieno[2,3-*c*]pyridine-2-carboxamides: Substituent Effects of the Aryloxy Group



Compound	R^1	R^2	R^3	CAM ELISA IC_{50} ± sem,[a] nM			Toxicity IC_{50} ± sem,[a] μM
				E-Selectin	ICAM-1	VCAM-1	(HUVEC, MTS)
15	Cl	H	H	6 ± 0.5	9 ± 1	>1000	55
21	H	Cl	H	800 ± 15	770 ± 30	850 ± 30	nd[b]
22	H	Br	H	80 ± 20	110 ± 10	>1000	nd
23	H	CF_3	H	870 ± 30	760 ± 30	>1000	nd
24	H	CO_2Et	H	630 ± 15	680 ± 25	>1000	nd
25	Cl	CH_3	H	70 ± 3	82 ± 19	>1000	67±12
26	CH_3	Cl	H	170 ± 5	150 ± 0	>1000	nd
27	Cl	F	H	8 ± 0	10 ± 6	>1000	nd
28	H	3,5-$(CH_3)_2$	H	>1000	>1000	>1000	nd
29	Cl	H	CH_3	370 ± 0	580 ± 440	>1000	nd
30	Cl	H	Br	110 ± 40	300 ± 240	330	nd
31	H	H	Allyl	940 ± 60	780 ± 0	780 ± 0	nd
32	H	H		>1000	>1000	>1000	nd

[a] Values for triplicate assay. SEM for multiple triplicate determinations. [b] Value not determined.

tors, we considered using an acryloyl as a linker to attach the water-solubilizing group to the *para*-position of the 4-phenoxy group. As illustrated in Table 4, installation of a morpholine acrylamide (**66**), and 2-morpholin-4-ylethyl acrylamide (**67**, **68**) provided inhibitors which retained acceptable in vitro activity. Attachment of a 3-aminopropanediol (**69**, **70**), [2-[bis(2-hydroxyethyl)amino]ethyl]amine (**71**, **72**), and 4-(2-aminoethyl)-imidazole (**73**), however, resulted in the loss of most of the potency. Given that the *p*-acetyl analogue **48** and ethoxycarbonyl analogue **49** still had good in vitro potencies, we next pursued an amide linkage. Unfortunately, compounds **74**−**79** bearing a *p*-carboxamide linkage only retained weak activity (>0.77 μM for E-selectin). Installation of polyethers and alcohols as water-solubilizing groups using a CH_2 linkage as exemplified in **80**−**88** provided potent inhibitors against E-selectin and ICAM-1 expression (IC_{50} = 5−28 nM), except for **84**, which had a branching hydroxy group on the linker. As shown in Table 4, their aqueous solubilities (pH 7.4) were improved compared to that of **15** or **40**, up to 160 μg/mL for **87**.

Since **87** is very potent (IC_{50} = 5 nM for E-selectin), selective (>200-fold over VCAM-1 expression), and fairly aqueous soluble, its pharmacokinetic behavior was evaluated. Figure 2 shows the poor PK profile of **87** (A-270063) in rats, with a short half-life and low drug concentration.

When **87**'s close analogue **86** was incubated with rat hepatocytes at 200 μM for 24 h, LC/MS and LC/MS/MS analyses of the mixture suggested the presence of **89**, **90**, **85**, **91**, and **92** (Scheme 5). Metabolites **89**, **90**, and **85** were also identical with an authentic sample on HPLC.

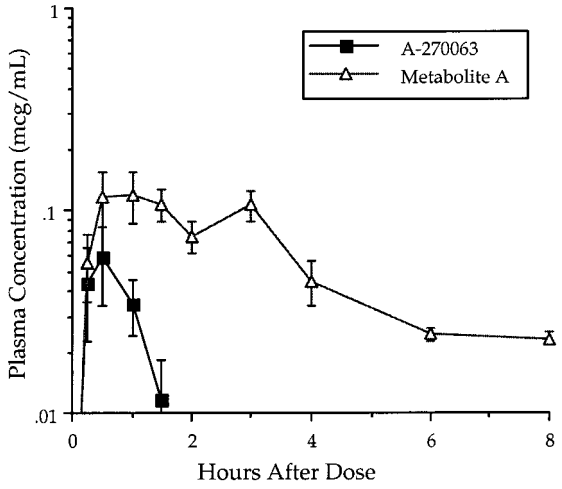
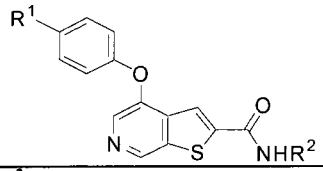


Figure 2. Pharmacokinetics of **87** (oral dose 5 mg/kg): short half-life, low drug concentration, and more metabolites.

Detection of metabolites **89** and **91** indicated that the glycol moiety was a site of metabolism for this series of compounds through benzylic oxidation and demethylation. As observed in other thienopyridine inhibitors, dealkylated **85** and hydrolyzed **90** were also observed for **86**. To increase the metabolic stability of this series of inhibitors, we envisioned that installation of a cyclopropane protection at the benzylic position and replacement of the terminal methyl group with a more stable ethyl group would suppress the benzylic oxidation and dealkylation of the glycol side chain. As illustrated in Table 5, cyclopropane **93** (IC_{50} = 46 nM for ICAM-1)

Table 3. In Vitro Potencies and Cellular Toxicities of 4-Substituted Thieno[2,3-*c*]pyridine-2-carboxamides: Steric and Electronic Effects of the *para*-Substitutions



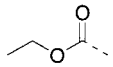
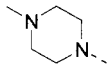
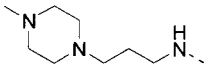
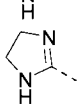
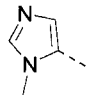
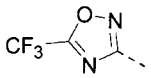
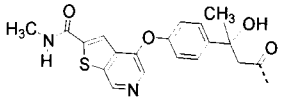
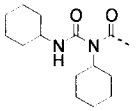
Compound	R^1	R^2	CAM ELISA IC_{50} ± sem,[a] nM			Toxicity IC_{50} ± sem,[a] μM
			E-Selectin	ICAM-1	VCAM-1	(HUVEC, MTS)
33	H	H	60 ± 20	120 ± 25	>1000	nd[b]
34	CH_2=CH	H	1 ± 0	2 ± 1	6, >1000	>10
35	C_2H_5	H	30 ± 0	20 ± 0	140	>10
36	$(CH_3)_2CH$	H	76 ± 3	47 ± 1	>100	34±3
37	$(CH_3)_3C$	H	79 ± 40	110 ± 40	>4000	87, >100
38	$CH_3(CH_2)_6CH_2$	H	520 ± 100	490 ± 90	>4000	>100
39	F	H	100 ± 40	160 ± 30	153, >200	nd
15	Cl	H	6 ± 0.5	9 ± 1	3900 ± 100	55±0
40	Br	H	4 ± 1	5 ± 1	48 ± 14	>100
41	I	H	6 ± 0.2	4 ± 0.8	>10	nd
42	CF_3	H	19 ± 1	13 ± 3	>100	71±5
43	NC	H	3 ± 1	2 ± 1	85 ± 42	nd
16	Cl	CH_3	8 ± 0.5	17 ± 10	>1000	nd
44	Br	CH_3	7 ± 1	5 ± 1	>1000	>100
45	CF_3	CH_3	0.7 ± 0	1 ± 1	>1000	nd
11	NC	CH_3	18 ± 13	18± 16	91 ± 89	nd
46	CH_3O	H	150 ± 30	430 ± 290	>1000	nd
47	CF_3O	CH_3	60 ± 39	53 ± 31	370 ± 30	nd
48		CH_3	21 ± 6	40 ± 19	>1000	nd
49		H	20 ± 6	18 ± 3	>1000	nd
50	H_2N	H	35 ± 3	42 ± 8	64 ± 13	nd
51		H	380 ± 220	150 ± 14	>1000	nd
12c		CH_3	13 ±11	59 ± 48	>1000	>10
52		CH_3	35 ± 1	79 ± 14	>1000	nd
53		CH_3	110 ± 6	120 ± 5	>1000	nd
54		CH_3	120 ± 15	120 ± 14	>1000	nd
55		H	6 ± 2	5 ± 1	17 ± 5	nd
56		CH_3	2 ± 1	6 ± 8	19 ± 9	>10
57		CH_3	4 ± 1	4 ± 2	5 ± 1	nd
58		CH_3	180 ± 120	160 ± 120	240 ± 210	nd
12b		CH_3	>1000	>1000	>1000	nd
12a		CH_3	470 ± 110	970, >1000	>1000	nd

Table 3 (Continued)

Compound	R^1	R^2	CAM ELISA $IC_{50} \pm$ sem,[a] nM			Toxicity $IC_{50} \pm$ sem,[a] μM
			E-Selectin	ICAM-1	VCAM-1	(HUVEC, MTS)
59		CH_3	150 ± 13	360 ± 380	180, >1000	nd
60		CH_3	28 ± 11	22 ± 23	>1000	nd
61		CH_3	9 ± 3	25 ± 21	79 ± 25	nd
62		CH_3	5 ± 3	6 ± 6	6 ± 2	nd
63		CH_3	5 ± 1	5 ± 1	>1000	nd
64		CH_3	2.8 ± 0.9	3.8 ± 1.4	>1000	nd
65		H	115 ± 42	116 ± 43	>1000	nd

[a] Values for triplicate assay. SEM for multiple triplicate determinations. [b] Value not determined.

was only slightly less potent than **83**. The polyether analogue **94** was 20-fold less potent against both E-selectin and ICAM-1 expression versus its close relative **87**. To our surprise, the difluoromethyl derivatives **10f** and **95** suffered a significant loss of in vitro potencies compared to the dihydro analogues **83** and **88**.

The elevated expression of cell adhesion molecules is due primarily to upregulation of the gene transcription, resulting in the de novo synthesis of these proteins. As has been recently described,[22,23,24] diverse signals act on endothelial cells to activate members of the nuclear factor of κB (NF-κB) transcription factor family. We conducted a number of assays to assess mRNA synthesis (RNA slot blots) and NF-κB activation (Western blots & gel shift experiments). These compounds, as a class, selectively inhibited E-selectin and ICAM-1 transcription (but not VCAM or GAPDH). Phosphorylation of NF-κB was not inhibited, and translocation of NF-κB to the nucleus was only modestly inhibited. In a further effort to explore the targeting proteins of our lead compounds, we performed two sets of experiments to evaluate direct interaction of our lead compounds with regular HUVEC cell lysates and with those whose cell adhesion molecule expression was induced by TNFα. In the first experiment, [^{3}H]**33** and [^{125}I]**41** were incubated with HUVEC cell lysates for 2 and 18 h, and subjected to a BioRad P30 spin column assay. The void volume containing molecules with molecular weight >40000 was collected after centrifugation at 600*g* for 4 min. Less than 0.1% radioactivity was detected in the void volume, demonstrating lack of interaction of our lead inhibitors with any molecule with a molecular weight of 40000 or greater in the HUVEC cell lysates. In the second experiment, [^{3}H]**33** and [^{125}I]**41** were incubated with HUVECs under standard conditions. After TNFα induction, the cells were fractionated according to a modified protocol by Goldstein et al.[25] The cytoplasm contained less than 1% radioactivity, the remaining counts localized to the nucleus. Gel filtration of the nuclear fraction revealed that these lead inhibitors were associated with macromolecules of a molecular weight greater than 650000 (Figure 3).

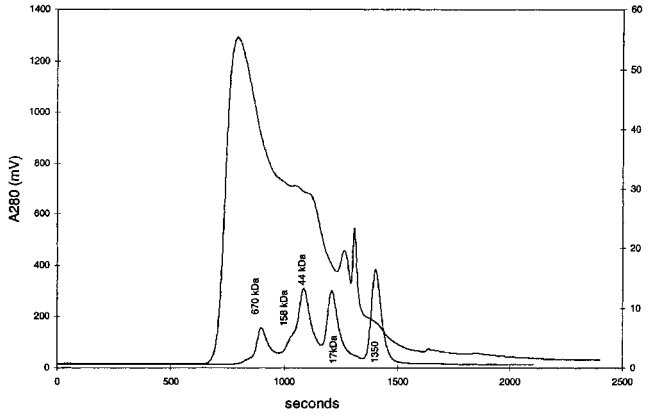
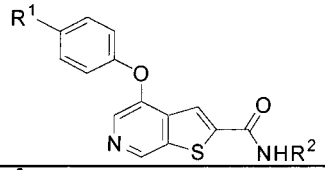


Figure 3. Gel filtration of the nuclear fraction of [^{3}H]**33**-treated HUVECs. The major peak associated with [^{3}H]**33** had a molecular weight greater than 650000. The gel filtration was performed on a Beckman Gold HPLC chromatography system with a SynChropak GPC-300 column (250 × 4.6 mm). Mobile phase: 20 mM sodium phosphate (pH 7.4) with 135 mM NaCl. Flow rate: 100 μL/min.

Since the enzymes that are involved in the signaling pathways leading to activation of adhesion molecule expression were not available to us, the ability of a series of structurally diverse compounds such as **1**, **40**, **16**, and **88** to inhibit interleukin-1β (IL-1β) or phorbol myristate acetate (PMA) induced CAM expression on HUVEC was investigated, using the same protocol as described for TNFα-induced expression to support a

Table 4. In Vitro Potencies and Cellular Toxicities of 4-Substituted Thieno[2,3-*c*]pyridine-2-carboxamides: Introduction of a Water-Solubilizing Functionality at the *para*-Position of the 4-Aryloxy Group



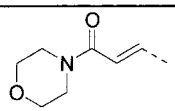
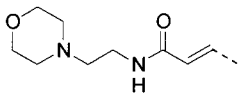
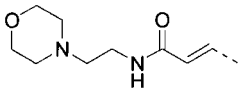
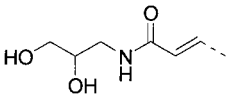
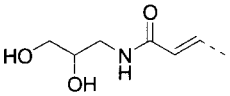
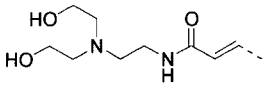
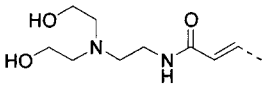
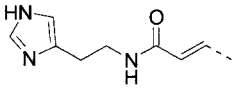
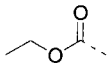
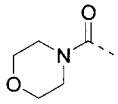
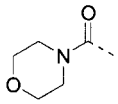
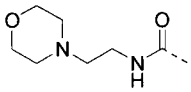
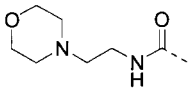
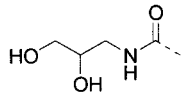
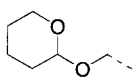
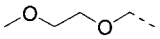
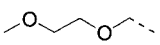
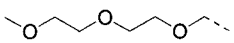
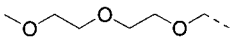
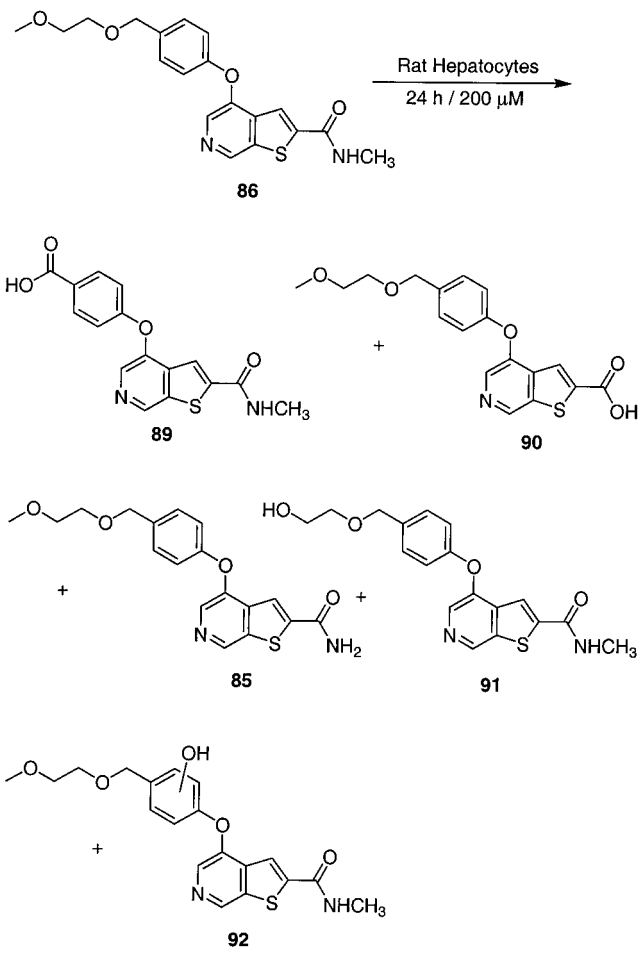
Compound	R^1	R^2	CAM ELISA IC_{50} ± sem,[a] nM			Solubility μg/mL
			E-Selectin	ICAM-1	VCAM-1	pH 7.4 buffer
66		H	25 ± 2	16 ± 6	140, >1000	nd[b]
67		H	34 ± 1	32 ± 2	>1000	nd
68		CH_3	43 ± 3	53 ± 18	>1000	nd
69		H	715, >1000	790 ± 80	>1000	nd
70		CH_3	830 ± 30	580 ± 70	>1000	nd
71		H	650 ± 20	820 ± 40	>1000	nd
72		CH_3	680 ± 32	600 ± 20	>1000	nd
73		CH_3	600 ± 47	670 ± 130	>1000	nd
47		CH_3	21 ± 6	40 ± 19	>1000	nd
48		H	20 ± 6	18 ± 3	>1000	nd
74		H	870 ± 156	830 ± 49	>1000	nd
75		CH_3	864 ± 9	901, >1000	>1000	nd
76		H	>1000	>1000	>1000	decomposed on HPLC
77		CH_3	770 ± 30	730 ± 30	>1000	decomposed on HPLC
78		H	>1000	>1000	>1000	nd
79		H	2 ± 1	1.4 ± 0.2	>1000	nd
40	Br	H	4 ± 1	5 ± 1	48 ± 14	0.46

Table 4 (Continued)

Compound	R^1	R^2	CAM ELISA IC_{50} ± sem,[a] nM			Solubility µg/mL
			E-Selectin	ICAM-1	VCAM-1	pH 7.4 buffer
80		H	16 ± 4	16 ± 4	23 ± 4	6.2
81		CH_3	13 ± 4	17 ± 5	24, >1000	4.8
82		H	28 ± 3	23 ± 3	191	6.9
83		CH_3	25 ± 12	31 ± 0.2	>1000	nd
84		H	670 ± 35	680 ± 56	930	15.3
85		H	5 ± 0.4	6	>1000	nd
86		CH_3	7 ± 0	8 ± 0.7	>1000	25.7
87		H	5 ± 0.6	4 ± 0.5	>1000	160
88		CH_3	6 ± 0	5 ± 2	120 ± 70	nd

[a] Values for triplicate assay. SEM for multiple triplicate determinations. [b] Value not determined.

Scheme 5



common mechanism of our lead molecules. As shown in Table 6, all compounds inhibited the IL-1β-induced expression of E-selectin and ICAM-1 with essentially the same level of potency as that for TNFα-induced expression. For reasons which are unclear, the ability of these compounds to inhibit PMA-induced E-selectin expression was significantly reduced. Inhibition of ICAM-1 and VCAM-1 expression by each compound, however, was similar regardless of the inducer utilized. This result suggests that PMA may activate E-selectin expression via two (or more) pathways, (at least) one of which is not subject to inhibition by these compounds.

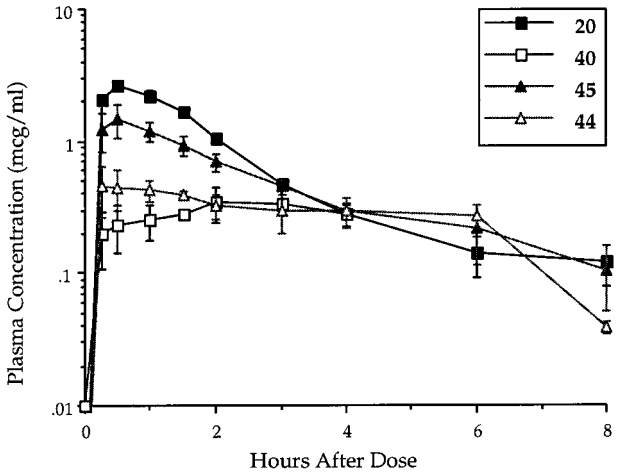


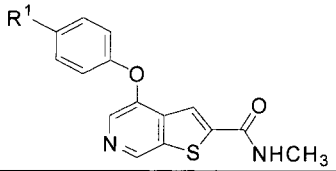
Figure 4. Pharmacokinetics of compounds **20**, **40**, **44**, and **45** (oral dose 5 mg/kg): comparison of the parent drug concentration.

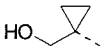
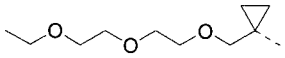
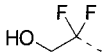
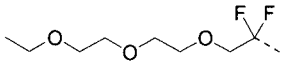
In Vivo Animal Model Discussion

A combined evaluation of an in vitro potency, selectivity, and pharmacokinetic behavior of the more potent thienopyridine inhibitors revealed that compounds **20**, **40**, **44**, and **45** were adequate for preliminary animal model studies. Figure 4 shows the concentrations of parent drugs for the four compounds in rat plasma after oral administration.

All of these compounds retained a plasma drug concentration of more than 100 times their IC_{50} against both E-selectin and ICAM-1 expression for 12 h following oral administration (25 mg/kg). In a rat rheumatoid arthritis model,[26] all rats were treated with peptidoglycan polysaccharide (PGPS) to elicit the disease to a desired degree. Six rats per group were then treated with compounds **20**, **40**, and **44** (25 mg/kg) or vehicle control twice daily. All compounds were formulated in 0.2% methylcellulose. The ankles of these rats were measured on day 0, 1, 3, 7, 9, 11, 16, 18, and 21 after administration. Histologic analyses of the ankles were performed on the last day of the experiment.

Table 5. In Vitro Potencies and Cellular Toxicities of 4-Substituted Thieno[2,3-*c*]pyridine-2-carboxamides: Benzylic Substitutions for Increased Metabolic Stability



Compound	R^1	CAM ELISA IC_{50} ± sem,[a] nM			Toxicity IC_{50} ± sem,[a] μM
		E-Selectin	ICAM-1	VCAM-1	(HUVEC, MTS)
83		25 ± 12	31 ± 0.2	>1000	nd[b]
93		31 ± 16	46 ± 53	74 ± 53	nd
94		120 ± 40	130 ± 30	420	>10
45		0.7 ± 0	1 ± 1	>1000	>10
10f		300 ± 560	320 ± 360	470 ± 30	nd
95		110 ± 50	26 ± 15	170	nd

[a] Values for triplicate assay. SEM for multiple triplicate determinations. [b] Value not determined.

Table 6. Comparison of in Vitro Potencies of **1**, **40**, **16**, and **88** against TNFα-, IL-1β-, and PMA-Induced CAM Expression

		CAM ELISA (IC_{50}, nM)		
compd	inducer	E-selectin	ICAM-1	VCAM-1
1	TNF	15	15	40
	IL-1β	25	10	35
	PMA	44% (1)[a]	30	45% (1)[a]
40	TNF	4	3	8
	IL-1β	6	3	7
	PMA	48% (1)[a]	6	20
16	TNF	20	15	49% (1)[a]
	IL-1β	25	10	70
	PMA	43% (1)[a]	15	200
88	TNF	4	5	30
	IL-1β	5	2	20
	PMA	46% (1)[a]	5	20

[a] Inhibition at 1 μM

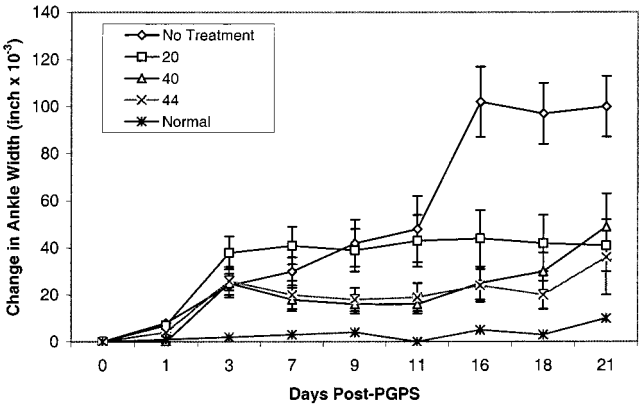


Figure 5. PGPS-elicited rat rheumatoid arthritis model for compounds **20**, **40**, and **44** (oral dose 25 mg/kg): change in ankle width.

Figure 5 shows the change in ankle width of compound-treated or vehicle-controlled rats versus untreated and normal animals on the recorded days. It was clear that all three compounds significantly reduced the width of inflamed ankles after the ninth day following

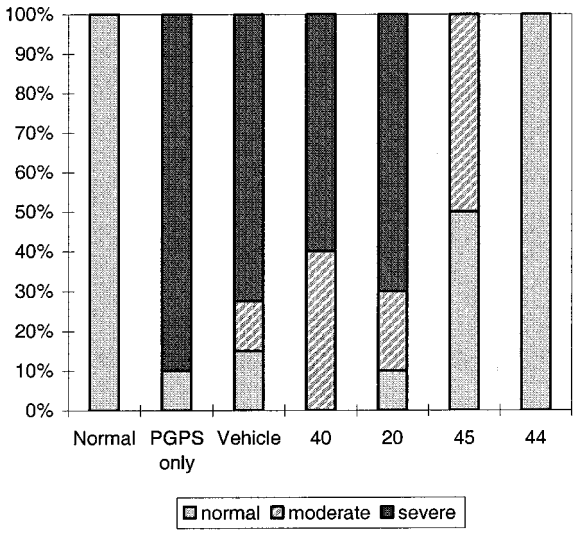


Figure 6. Histology scoring of compounds **40**, **20**, **45**, and **44** for the rat PGPS rheumatoid arthritis model (oral dose 25 mg/kg).

treatment. None of the compounds showed efficacy in the acute phase (before day 3). Compounds **40** and **44** were more efficacious in the chronic phase, while modest efficacy was observed for compound **20**. At the study termination, the histopathology of the ankle joints was graded in a blinded fashion on a subjective scale based on the extent of cellular infiltration, fibrosis, edema, cartilage degeneration, and bone erosion. Joints considered "normal" had minimal or no cellular infiltrate, fibrosis, or edema. "Moderate" changes included infiltration of the synovium with small numbers of inflammatory cells, mild to moderate edema, mild or rare bone remodeling, fibrosis or pannus formation, and mild to moderate degeneration of articular cartilage. Joints graded as "severe" had numerous inflammatory cells in the synovium and joint space, severe edema, and severe lysis of bone and cartilage with collapse of the joint

Table 7. Efficacy of Inhibitors **40**, **20**, **45**, and **44** in an Inhaled Allergen-Induced Cell Influx in Mice after Oral Dosing

treatment[a]	N	dose (mg/kg)	lavage cells (no./μL)[b]	neutrophils (%)[b]	eosinophils (%)[b]	serum sICAM-1 (μg/mL; 24 h post Ag)[b]	BAL sICAM-1 (μg/mL; 24 h post Ag)[b]
naive (− ctrl)	4		59 ± 8	22 ± 1	0 ± 0	17.8 ± 1.3	1.69 ± 0.10
Vehicle (+ ctrl)	6		86 ± 4	40 ± 7	25 ± 3	19.5 ± 0.7	1.92 ± 0.16
40	6	30	93 ± 12	38 ± 6	8 ± 2[d]	18.8 ± 1.0	1.74 ± 0.15[e]
20	6	30	119 ± 7	45 ± 5	23 ± 5	19.1 ± 0.6	1.95 ± 0.10
45	7	30	107 ± 10	48 ± 7	10 ± 3[d]	19.6 ± 0.7	1.89 ± 0.15
44	7	30	98 ± 12	41 ± 5	13 ± 2[e]	19.0 ± 0.4	1.66 ± 0.13
naive (− ctrl)[c]	4		84 ± 5	4 ± 1	1 ± 1	17.3 ± 0.4	1.53 ± 0.08
vehicle (+ ctrl)[c]	6		322 ± 27	58 ± 6	17 ± 5	21.8 ± 0.7	2.64 ± 0.18
40[c]	6	30	288 ± 32	57 ± 4	9 ± 2[g]	18.5 ± 0.5[f]	1.99 ± 0.07[f]
40[c]	7	3	319 ± 31	60 ± 3	14 ± 2	21.3 ± 0.7	2.68 ± 0.17
40[c]	7	0.3	282 ± 41	44 ± 5	19 ± 2	20.7 ± 0.7	2.67 ± 0.18

[a] Compounds and vehicle (0.2% methylcellulose) dosed at −18 and −1 relative to the first of two allergen inhalations. Lung lavage at 24−27 h after the first allergen inhalation. [b] All values are mean ± SE. sICAM-1 = soluble ICAM-1. [c] Separate experiment. [d] Significantly different ($p < 0.001$) from positive control. [e] Significantly different ($p < 0.01$) from positive control. [f] Significantly different ($p < 0.005$) from positive control. [g] $p = 0.08$ versus positive control.

architecture. The overall ratings were scored and are summarized in Figure 6.

As illustrated in Figure 6, treatment with compound **44** (25 mg/kg) for 21 days significantly reduced the ankle inflammation of the arthritis rats. Some reduction of the inflammation was observed for compounds **20** and **40**, and agreed with the efficacy shown in reduction of ankle width.

We also examined the efficacy of selected inhibitors in a mouse asthma model.[27] Compounds **40**, **20**, **45**, and **44** and vehicle (0.2% methylcellulose) were dosed at 18 and 1 h prior to the first of two allergen inhalations. The lungs were lavaged at 24−27 h after the first allergen inhalation, and cell counts were obtained in the lavage fluid. Table 7 shows the inhaled allergen-induced cell influx for compounds **40**, **20**, **45**, and **44**. Significant reduction of eosinophils and serum-soluble ICAM-1 (sICAM-1) was observed for compounds **40**, **45**, and **44**. This reduction was dose-dependent for **40** at 30, 3, and 0.3 mg/kg. No efficacy against neutrophil influx was detected for any of the compounds tested.

Conclusion

We have extensively explored the SAR of the 4-position of our lead thieno[2,3-*c*]pyridine series. We found that replacement of the C-4 sulfur linkage of the original lead inhibitor A-205804 (**1**) with an oxygen atom increased in vitro potency and eliminated one of the two major metabolic pathways of the lead molecule. Substituents at the *para*-position of the 4-phenoxy group were found to be the most critical to impart higher in vitro potencies and selectivities for E-selectin and ICAM-1 over VCAM-1 expression inhibition. *Ortho*- and *meta*-substituted phenoxy analogues were less potent. A variety of water-solubilizing groups were installed at the *para*-position of the 4-phenoxy group and provided potent inhibitors, but the pharmacokinetic behavior was poor. A balanced comparison of in vitro potency, pharmacokinetics profile, and physical properties led to the selection of **20**, **40**, **44**, and **45** as candidates for in vivo pharmacology. All of these compounds showed significant efficacy in a rat rheumatoid arthritis model and in a mouse asthma model.

Experimental Section

General Spectroscopic and Experimental Data. The NMR spectra were obtained on Varian UP-300, Varian M-300, Bruker AMX-400, and Varian U-400 magnetic resonance spectrometers (300/400 MHz for ^{1}H and 75/100 MHz for ^{13}C) with deuteriochloroform as solvent and internal standard unless otherwise indicated. The chemical shifts are given in δ values and the coupling constants (J) in hertz (Hz). Infrared spectra were recorded on Nicolet 5SX and Nicolet Magna-IR 750 spectrometers. Mass spectral analyses were accomplished using different techniques, including desorption chemical ionization (DCI), atmospheric pressure chemical ionization (APCI), and electrospray ionization (ESI), as specified for individual compounds. Elemental analysis was performed by Robertson Microlit Laboratories, Inc., Madison, NJ. All manipulations were performed under nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Flash column chromatography was performed on silica gel 60 (Merck, 230−400 mesh) using the indicated solvent. Preparative HPLC was performed on an automated Gilson HPLC system equipped with a Zorbax C-18 column (2.54 × 250 cm, 5 μm). Mobile phase A was 0.1% TFA in H_2O. Mobile phase B was 0.1% TFA in CH_3CN. For routine aqueous workup, the reaction mixtures were partitioned between water and EtOAc, and the organic layer was washed with brine and dried over $MgSO_4$.

General Method for the Synthesis of Methyl 4-(Aryloxy)thieno[2,3-*c*]pyridine-2-carboxylate 6. A solution of the appropriate phenol (20 mmol) in THF (20 mL) was treated with a solution of potassium *tert*-butoxide (1.0 M solution in THF, 20 mL, 20 mmol) at 0 °C. This solution was stirred at 25 °C for 1 h and was cooled to 0 °C. A solution of 3,5-dichloropyridine-4-carboxaldehyde (**4**) (10 mmol) in THF (10 mL) was added, and the reaction mixture was heated at 70 °C for 2 h. After the reaction mixture was cooled to 0 °C, methyl thioglycolate (10 mmol) and Cs_2CO_3 (10 mmol) were added. The mixture was heated at 70 °C for 0.5 h, cooled to room temperature, and filtered. The filtrate was diluted with ethyl acetate, washed sequentially with water and brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel provided **6**.

General Method for the Synthesis of 4-(Aryloxy)-thieno[2,3-*c*]pyridine-2-carboxamide 8. Method A. **6** (5 mmol) was dissolved in 2 M methanolic ammonia (50 mL) and warmed to 45 °C in a sealed tube for 18 h. The precipitate was filtered, washed with methanol/diethyl ether (1:1), and dried under vacuum to give amide **8**. The mother liquor was concentrated, and the residual material was purified by flash chromatography to provide additional **8**.

Method B. A solution of methyl ester **6** (10 mmol) in 1:1 THF/H_2O (100 mL) was treated with LiOH (20 mmol) at room temperature until the reaction was complete, as judged by TLC or HPLC. The reaction mixture was then acidified with 10% HCl to pH 3, and concentrated to remove most of the organic solvents. The formed solid was collected by filtration, washed with water, and dried to give acid **7**. To a solution of the acid **7** (1 mmol) and requite amine (1.5 mmol) in DMF (10 mL) were

added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (1.5 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (1.5 mmol), and triethylamine (1.5 mmol). The reaction mixture was stirred at room temperature for 15 h, and then partitioned between ethyl acetate and brine. The organic phase was washed with water, dried, and concentrated. The residual material was purified by flash chromatography on silica gel to give **8**.

Data for Methyl 4-(4-Bromophenoxy)thieno[2,3-*c*]-pyridine-2-carboxylate (9a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 6.97 (d, J = 8.8 Hz, 2H), 7.450 (d, J = 8.8 Hz, 2H), 8.08 (s, 1H), 8.17 (s, 1H), 8.98 (s, 1H); MS (DCI) *m/z* 364, 366 $(M + H)^+$. Anal. ($C_{15}H_{10}BrNO_3S$) C, H, N.

Data for 4-(4-Iodophenoxy)-*N*-methylthieno[2,3-*c*]-pyridine-2-carboxamide (9b): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.81 (d, J = 4.8 Hz, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H), 8.22 (s, 1H), 8.96 (q, J = 4.8 Hz, 1H), 9.18 (s, 1H); MS (DCI/NH_3) *m/e* 411 $(M + H)^+$. Anal. ($C_{15}H_{11}N_2IO_2S$) C, H, N.

Methyl 4-(4-Carboxyphenoxy)thieno[2, 3-*c*]pyridine-2-carboxylate (10c). A suspension of bromide **9a** (1.0 g, 2.74 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (0.284 g), and triethylamine (0.55 g) in a mixture of THF (15 mL) and H_2O (15 mL) was heated at 130 °C under a CO atmosphere (400 psi) for 19 h. EtOAc (200 mL) was added, and the mixture was washed with brine, dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 5% CH_3OH/CH_2Cl_2 to give **10c** (311 mg, 34%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.91 (s, 3H), 7.18 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 8.40 (s, 1H), 9.33 (s, 1H); MS (DCI/NH_3) *m/e* 330 $(M + H)^+$. Anal. ($C_{16}H_{11}NO_5S$) C, H, N.

Methyl 4-{4-[(*E*)-3-(*tert*-Butyloxy)-3-oxo-1-propenyl]-phenoxy}thieno[2,3-*c*]pyridine-2-carboxylate (10d). A flask charged with bromide **9a** (500 mg, 1.37 mmol), $Pd_2(dba)_3$ (63 mg, 0.069 mmol), and tri-*o*-tolylphosphine (64 mg, 0.21 mmol) was purged with nitrogen. Dry degassed DMF (20 mL), *tert*-butyl acrylate (602 μL, 4.11 mmol), and triethylamine (575 μL, 4.11 mmol) were added. This suspension was stirred at 100 °C for 12 h, and was partitioned between ethyl acetate and brine. The organic phase was washed with water, dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 20% EtOAc/hexane to give **10d** (323 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 3.98 (s, 3H), 6.33 (d, J = 15.5 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 15.5 Hz, 1H), 8.08 (s, 1H), 8.22 (br s, 1H), 9.00 (br s, 1H); MS (DCI/NH_3) *m/e* 412 $(M + H)^+$. Anal. ($C_{22}H_{21}NO_5S$) C, H, N.

4-{4-[1,1-Difluoro-1-(ethoxycarbonyl)methyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (10e). A suspension of activated copper (512 mg, 8 mmol) in dry DMSO (5 mL) was treated with ethyl iododifluoroacetate (1.0 g, 4 mmol) at room temperature for 10 min. Phenol (188 mg, 2 mmol) and **9b** were then added. The reaction mixture was stirred at room temperature for 20 h. After being diluted with 1:1 ether/EtOAc, the mixture was washed with 1% HCl in brine and water, dried ($MgSO_4$), and concentrated. The residue was separated by flash chromatography on silica gel (65% EtOAc/hexane), and was further purified by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to provide **10e** (85 mg, 15%). The obtained compound was still not pure enough as an analytical sample, and was directly used for the next step without further purification.

4-[4-(1,1-Difluoro-2-hydroxyethyl)phenoxy]-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (10f). A solution of **10e** (40 mg, 0.1 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (50 mg) at room temperature for 2 h. Brine was added, and the mixture was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to provide **10f** (44.4 mg, 94%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.94 (s, 3H), 3.93 (t, J = 13.5 Hz, 2H), 7.27 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 9.2 Hz, 2H), 8.15 (s, 2H), 9.24 (s, 1H); MS (ESI/NH_3) *m/e* 365 $(M + H)^+$. Anal. ($C_{17}H_{14}N_2O_3SF_2$·TFA) C, H, N.

4-(4-Cyanophenoxy)-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (11). 11 was prepared from **4** as described in the general synthesis of **8**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 (d, J = 4.4 Hz, 3H), 7.20 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.97 (s, 1H), 8.37 (s, 1H), 8.94 (q, J = 4.4 Hz, 1H), 9.26 (s, 1H); MS (ESI/NH_3) *m/e* 310 $(M + H)^+$. Anal. ($C_{16}H_{11}N_3O_2S$·0.05CH_2Cl_2) C, H, N.

4-[4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenoxy]-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (12a). A solution of **11** (800 mg, 2.6 mmol) in a mixture of MeOH (30 mL), Et_2O (20 mL), and CH_2Cl_2 (30 mL) was treated with hydrogen chloride gas at 0 °C for 1.5 h. After being warmed to room temperature for 24 h with stirring, the reaction mixture was concentrated. The residue was dissolved in MeOH (30 mL) and ethylenediamine (3 mL), and was heated at 70 °C for 2 h. After the solution was cooled to room temperature, the resultant white solid was collected by filtration, washed with methanol, and dried to provide **12a** (804 mg, 88%): mp > 280 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 (d, J = 4.4 Hz, 3H), 3.32 (br s, 4H), 6.88 (br s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 8.04 (s, 1H), 8.22 (s, 2H), 8.93 (q, J = 4.4 Hz, 1H), 9.17 (s, 1H); MS (ESI/NH_3) *m/e* 353 $(M + H)^+$. Anal. ($C_{18}H_{16}N_4O_2S$) C, H, N.

4-[4-(Tetrazol-5-yl)phenoxy]-*N*-methylthieno[2,3-*c*]-pyridine-2-carboxamide (12b). To a solution of **11** (30 mg, 0.097 mmol) in NMP (4 mL) were added NaN_3 (41 mg, 0.64 mmol) and triethylamine hydrochloride (4 mg, 0.32 mmol) at room temperature. This mixture was purged with nitrogen, and heated at 150 °C for 12 h. The reaction mixture was filtered, and the filtrate was directly purified by HPLC (C-18) to afford **12b** (51 mg, 90%): mp 126−128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.81 (d, J = 4.4 Hz, 3H), 7.32 (d, J = 8.8 Hz, 2H), 8.08 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 8.40 (s, 1H), 8.98 (q, J = 4.4 Hz, 1H), 9.30 (s, 1H); MS (ESI/NH_3) *m/e* 353 $(M + H)^+$. Anal. ($C_{16}H_{12}N_6O_2S$·1.3TFA) C, H, N.

***N*-Methyl-4-[4-(*N*-hydroxyamidino)phenoxy]thieno-[2, 3-*c*]pyridine-2-carboxamide (12c).** A solution of nitrile **11** (500 mg, 1.62 mmol) in a mixture of DMF (10 mL) and EtOH (10 mL) was treated with triethylamine (279 mg, 2.75 mmol) and hydroxylamine hydrochloride (169 mg, 2.43 mmol) at room temperature for 18 h. The formed white solid was collected by filtration, washed with EtOH, and dried to provide **12c** (376 mg, 68%): mp 250−252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.4 Hz, 3H), 5.8 (br s, 2H), 7.05 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 8.05 (s, 1H), 8.20 (s, 1H), 9.00 (m, 1H), 9.20 (s, 1H), 9.60 (s, 1H); MS (ESI/NH_3) *m/e* 343 $(M + H)^+$. Anal. ($C_{16}H_{14}N_4O_3S$) C, H, N.

Compounds **14**−**47** were prepared from dichloropyridine-carboxaldehyde **4** as described in the general synthesis of **8**.

Data for 4-(4-Methylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (14): mp 196−197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3 H), 7.04 (m, 2 H), 7.25 (m, 2 H), 7.82 (br s, 1 H), 8.00 (s, 1 H), 8.21 (s, 1 H), 8.42 (br s, 1 H) 9.07 (s, 1 H); MS (DCI/NH_3) *m/z* 285 $(M + H)^+$, 302 $(M + NH_4)^+$. Anal. ($C_{15}H_{12}N_2O_2S$) C, H, N.

Data for 4-(4-Chlorophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (15): mp 176−177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.14 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), 7.85 (s, 1H), 8.15 (d, J = 2.5 Hz, 2H), 8.44 (s, 1H), 9.15 (s, 1H); MS (DCI/NH_3) *m/z* 305 $(M + H)^+$. Anal. ($C_{14}H_9ClN_2O_2S$·0.25H_2O) C, H, N.

Data for 4-(4-Chlorophenoxy)-*N*-methylthieno[2,3-*c*]-pyridine-2-carboxamide (16): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.5 Hz, 3H,), 7.13 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 8.06 (s, 1H), 8.19 (s, 1H), 8.94 (d, J = 4.5 Hz, 1H), 9.16 (s, 1H); ^{13}C NMR (400 Hz, DMSO-d_6) δ 29.55 (NCH_3), 118.98 (CH), 119.39 (CH), 127.66 (C), 1330.04 (CH), 133.118 (CH),137.40 (C), 137.90 (C), 141.39 (CH), 146.19 (C), 147.07 (C), 155.57 (C), 160.88 (CO); MS (APCI) *m/e* 319 $(M + H)^+$, 353 $(M + Cl)^-$.

Data for 4-(4-Chlorophenoxy)-*N*-ethylthieno[2,3-*c*]-pyridine-2-carboxamide (17): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 8 Hz, 3H), 3.30 (m, 2H), 7.14 (d, J = 9 Hz,

2H), 7.47 (d, $J = 9$ Hz, 2H, 8.13 (s, 1H), 8.17 (s, 1H), 8.91 (t, $J = 6$ Hz, 1H), 9.15 (s, 1H); MS (DCI/NH_3) *m/e* 333 $(M + H)^+$, 303.

Data for 4-(4-Chlorophenoxy)-*N*,*N*-dimethylthieno[2,3-*c*]pyridine-2-carboxamide (18): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.03 (br s, 3H), 3.12 (br s, 3H), 7.17 (d, $J = 7.5$ Hz, 2H), 7.46 (d, $J = 7.5$ Hz, 2H), 7.62 (s, 1H), 8.18 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (400 Hz, DMSO-d_6) δ 29.5, 119.8, 119.9, 127.8, 129.9, 133.0, 136.3, 136.3, 140.8,143.6,147.3,155.4, 162.3; MS (APCI) *m/e* 333 $(M + H)^+$.

Data for 4-(4-Chlorophenoxy)-*N*-(2-hydroxyethyl)-thieno[2,3-*c*]pyridine-2-carboxamide (19): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.33 (m, 2H), 3.51 (m, 2H), 5.76 (t, $J = 6.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 8.17 (s, 2H), 8.98 (br.t, $J = 6.0$ Hz, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.3, 59.4, 119.2, 119.3, 127.6, 130.0, 133.2, 137.5, 137.9, 141.4, 146.4, 147.1, 155.6, 160.6; MS (DCI/NH_3) *m/z* 349 $(M + H)^+$.

Data for 4-(4-Bromophenoxy)-*N*-(2-hydroxyethyl)-thieno[2,3-*c*]pyridine-2-carboxamide (20): mp 158−159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.32 (m, 2H), 3.51 (m, 3H), 4.79 (t, $J = 5.9$ Hz, 1H), 7.06 (d, $J = 8.8$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 2H), 8.17 (s, 1H), 8.20 (s, 1H), 9.02 (t, $J = 5.5$ Hz, 1H), 9.17 (s, 1H). MS (DCI/NH_3) *m/e* 393, 395 $(M + H)^+$. Anal. ($C_{16}H_{13}BrN_2O_3S$) C, H, N.

Data for 4-(3-Chlorophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (21): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.04 (m, 1H), 7.27 (m, 2H), 7.45 (br s, 1H), 7.87 (br s, 1H), 8.15 (d, 1H), 8.21 (s, 1H), 8.45 (br s, 1H), 9.18 (s, 1H); MS (DCI/NH_3) *m/z* 305 $(M + H)^+$.

Data for 4-(3-Bromophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (22): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.07 (dt, $J = 7.1$, 2.0 Hz, 1H), 7.36−7.39 (m, 3H), 7.87 (br s, 1H), 8.15 (s, 1H), 8.20 (s, 1H), 8.45 (br s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/z* 349, 351 $(M + H)^+$. Anal. ($C_{14}H_9N_2O_2S{\cdot}CH_3OH$) C, H, N.

Data for 4-[3-(Trifluoromethyl)phenoxy]thieno[2,3-*c*]-pyridine-2-carboxamide (23): mp 175−176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, $J = 3.7$ Hz, 3H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.55 (m, 2H), 7.65 (t, $J = 8.0$ Hz, 1H), 8.10 (s, 1H), 8.30 (s, 1H), 9.00 (br s, 2H), 9.25 (s, 1H); MS (DCI/NH_3) *m/e* 353 $(M + H)^+$. Anal. ($C_{16}H_{11}F_3N_2O_2S{\cdot}0.25\ H_2O$) C, H, N.

Data for Ethyl 3-{[2-(Aminocarbonyl)thieno[2,3-*c*]-pyridin-4-yl]oxy}benzoate (24): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, $J = 7.1$ Hz, 3 H), 4.31 (q, $J = 7.1$ Hz, 2 H), 7.39 (ddd, $J = 8.3$, 2.5, 1.0 Hz, 1 H), 7.58 (m, 2 H), 7.79 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.83 (br s, 1H), 8.15 (s, 1 H), 8.19 (s, 1 H), 8.42 (br s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/z* 343 $(M + H)^+$.

Data for 4-(4-Chloro-3-methylphenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (25): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 6.95 (dd, $J = 8.7$, 3.0 Hz, 1H), 6.97 (d, $J = 3.0$ Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 7.85 (br s, 1H), 8.13 (s, 1H), 8.16 (s, 1H), 8.45 (s, 1H), 9.14 (s, 1H); MS (DCI/NH_3) *m/z* 319 $(M + H)^+$.

Data for 4-(3-Chloro-4-methylphenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (26): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 7.00 (dd, $J = 8.4$, 2.6 Hz, 1H), 7.26 (d, $J = 2.6$ Hz, 1H), 7.39 (d, $J = 8.5$ Hz, 1H), 7.86 (br s, 1H), 8.13 (s, 1H), 8.17 (s, 1H), 8.45 (br s, 1H), 9.14 (s, 1H); MS (DCI/NH_3) *m/z* 319 $(M + H)^+$.

Data for 4-(4-Chloro-3-fluorophenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (27): mp 227−228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.94 (m,1H), 7.34 (dd, $J = 3.0$, 10.5 Hz, 1H), 7.60 (t, $J = 8.7$ Hz, 1H), 7.87 (s, 1H), 8.11 (s, 1H), 8.26 (s, 1H), 8.44 (s, 1H), 9.19 (s, 1H); MS (DCI/NH_3) *m/e* 323 $(M + H)^+$. Anal. ($C_{14}H_8N_2ClFO_2S$) C, H, N.

Data for 4-(3,5-Dimethylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (28): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.31 (s, 6H), 6.73 (s, 2H), 6.85 (s, 1H), 7.82 (br s, 1H), 8.05 (s, 1H), 8.18 (s, 1H), 8.43 (br s, 1H), 9.10 (s,1H); MS (DCI/NH_3) *m/z* 299 $(M + H)^+$.

Data for 4-(4-Chloro-2-methylphenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (29): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 6.95 (d, $J = 8.6$ Hz, 1H), 7.27 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.50 (d, $J = 2.6$ Hz, 1H), 7.88 (br s, 1H), 7.93 (s, 1H), 8.22 (s, 1H), 8.46 (br s, 1H), 9.09 (s, 1H); MS (DCI/NH_3) *m/z* 319 $(M + H)^+$.

Data for 4-(2-Bromo-4-chlorophenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (30): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18 (d, $J = 8.8$ Hz, 1H), 7.49 (dd, $J = 8.8$, 2.6 Hz, 1H), 7.90 (br s, 1H), 7.98 (s, 2H), 8.23 (s, 1H), 8.49 (br s, 1H), 9.14 (s, 1H); MS (DCI/NH_3) *m/z* 383 $(M + H)^+$. Anal. ($C_{14}H_8BrClN_2O_2S$) C, H, N.

Data for 4-[2-(2-Propenyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (31): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.43 (d, $J = 6.6$ Hz, 2H), 5.01 (m, 1H), 5.05 (m, 1H), 5.98 (ddt, $J = 17.6$, 10.0, 6.6 Hz, 1H), 7.00 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.27 (m, 2H), 7.39 (dd, $J = 7.4$, 1.9 Hz, 1H), 7.82 (s, 1H), 7.88 (br s, 1H), 8.27 (s, 1H), 8.49 (br s, 1H), 9.05 (s, 1H); MS (DCI/NH_3) *m/z* 311 $(M + H)^+$. Anal. ($C_{17}H_{14}N_2O_2S$) C, H, N.

Data for 4-[2-(2,3-Dihydroxypropyl)phenoxy]thieno-[2,3-*c*]pyridine-2-carboxamide (32): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (dd, $J = 13.4$, 8.4 Hz, 1H), 2.88 (dd, $J = 13.4$, 4.6 Hz, 1H), 3.29 (t, $J = 5.6$ Hz, 2H), 3.76 (m, 1H), 4.55 (t, $J = 5.1$ Hz, 1H), 4.63 (d, $J = 5.1$ Hz, 1H), 6.94 (dd, $J = 7.7$, 1.3 Hz, 1H), 7.22 (m, 2H), 7.45 (dd, 1H), 7.84 (s, 1H), 7.88 (br s, 1H), 8.26 (s, 1H), 8.46 (br s, 1H), 9.04 (s, 1H); MS (DCI/NH_3) *m/z* 345 $(M + H)^+$. Anal. ($C_{17}H_{16}N_2O_4S$) C, H, N.

Data for 4-Phenoxythieno[2,3-*c*]pyridine-2-carboxamide (33): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (dd, 2H), 7.20 (t, 1H), 7.45 (t, 2H), 7.85 (br s, 1H), 8.10 (s, 1H), 8.20 (s, 1H), 8.45 (br s, 1H), 9.15 (s, 1H); MS (DCI/NH_3) *m/z* 271 $(M + H)^+$. Anal. ($C_{14}H_{10}N_2O_2S$) C, H, N.

Data for 4-(4-Ethenylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (34): ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.24 (d, $J = 10.1$ Hz, 1H), 5.79 (d, $J = 17.6$ Hz, 1H), 6.75 (dd, $J = 17.6$, 10.1 Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.87 (br s, 1H), 8.12 (s, 1H), 8.18 (s, 1H), 8.45 (br s, 1H), 9.13 (s, 1H); MS (DCI/NH_3) *m/z* 297 $(M + H)^+$. Anal. ($C_{16}H_{12}N_2O_2S{\cdot}0.25CH_3OH$) C, H, N.

Data for 4-(4-Ethylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (35): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19 (t, $J = 7.5$ Hz, 3H), 2.62 (q, $J = 7.5$ Hz, 2H), 7.05 (dt, $J = 8.5$, 2.0 Hz, 2H), 7.26 (dt, $J = 8.5$, 2.0 Hz, 2H), 7.81 (br s, 1H), 8.07 (s, 1H), 8.21 (s, 1H), 8.43 (br s, 1H), 9.08 (s, 1H); MS (DCI/NH_3) *m/z* 299 $(M + H)^+$. Anal. ($C_{16}H_{14}N_2O_2S{\cdot}CH_3OH$) C, H, N.

Data for 4-[4-(1-Methylethyl)phenoxy]thieno[2,3-*c*]-pyridine-2-carboxamide (36): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (d, $J = 6.8$ Hz, 6H), 2.92 (septet, $J = 6.8$ Hz, 1H), 7.05 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.82 (br s, 1H), 8.03 (s, 1H), 8.21 (s, 1H), 8.44 (br s, 1H), 9.09 (s, 1H); MS (DCI/NH_3) *m/z* 313 $(M + H)^+$. Anal. ($C_{17}H_{16}N_2O_2S$) C, H, N.

Data for 4-(4-*tert*-Butylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (37): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (s, 9H), 7.04 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 7.82 (br s, 1H), 8.05 (s, 1H), 8.20 (s, 1H), 8.45 (br s, 1H), 9.09 (s, 1H); MS (DCI/NH_3) *m/z* 327 $(M + H)^+$.

Data for 4-(4-Octylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (38): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.22−1.38 (m, 10H), 1.62 (m, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 6.05 (br s, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 7.87 (s, 1H), 8.07 (br s, 1H), 8.92 (br s, 1H); MS (DCI/NH_3) *m/z* 383 $(M + H)^+$. Anal. ($C_{22}H_{26}N_2O_2S$) C, H, N.

Data for 4-(4-Fluorophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (39): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (m, 4 H), 7.87 (br s, 1H), 8.04 (s, 1H), 8.21 (s, 1 H), 8.45 (br s, 1H), 9.10 (s, 1H); MS (DCI/NH_3) *m/z* 289 $(M + H)^+$.

Data for 4-(4-Bromophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (40): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.08 (d, $J = 8.8$ Hz, 2H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.87 (br s, 1H), 8.14 (s, 1H), 8.17 (s, 1H), 8.45 (br s, 1H), 9.16 (s, 1H); MS (DCI/NH_3) *m/z* 349, 351 $(M + H)^+$. Anal. ($C_{14}H_9BrN_2O_2S{\cdot}0.75\ CH_3OH$) C, H, N.

Data for 4-(4-Iodophenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (41): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.94 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.86 (br s, 1H), 8.13 (s, 1H), 8.17 (s, 1H), 8.44 (br s, 1H), 9.16 (s, 1H); MS (DCI/NH_3) *m/z* 397 $(M + H)^+$. Anal. ($C_{14}H_9IN_2O_2S$) C, H, N.

Data for 4-[4-(Trifluoromethyl)phenoxy]thieno[2,3-*c*]-pyridine-2-carboxamide (42): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.24 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.88 (br s, 1H), 8.10 (s, 1H), 8.33 (s, 1H), 8.45 (br s, 1H), 9.24 (s, 1H); MS (DCI/NH_3) m/z 339 $(M + H)^+$. Anal. ($C_{15}H_9F_3N_2O_2S$) C, H, N.

Data for 4-(4-Cyanophenoxy)thieno[2, 3-*c*]pyridine-2-carboxamide (43): mp 255−257 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (d, J = 8.8 Hz, 2H), 7.84 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 8.05 (s, 1H), 8.36 (s, 1H), 8.41 (q, J = 4.4 Hz, 1H), 9.26 (s, 1H); MS (ESI/NH_3) m/e 296 $(M + H)^+$. Anal. ($C_{15}H_9N_3O_2S\cdot1.5CH_3OH$) C, H, N.

Data for *N*-Methyl-4-(4-Bromophenoxy)thieno[2,3-*c*]-pyridine-2-carboxamide (44): mp 78−80 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.8 Hz, 3H), 7.06 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H), 8.20 (s, 1H), 8.96 (q, J = 4.8 Hz, 1H), 9.17 (s, 1H); MS (DCI/NH_3) m/e 363,-365 $(M + H)^+$. Anal. ($C_{15}H_{11}BrN_2O_2S$) C, H, N.

Data for *N*-Methyl-4-[4-(trifluoromethyl)phenoxy]-thieno[2,3-*c*]pyridine-2-carboxamide (45): mp 157−158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 (d, J = 4.4 Hz, 3H), 7.22 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 8.01 (s, 1H), 8.34 (s, 1H), 8.92 (q, J = 4.4 Hz, 1H), 9.24 (s, 1H); MS (DCI/NH_3) m/e 353 $(M + H)^+$. Anal. ($C_{16}H_{11}F_3N_2O_2S$) C, H, N.

Data for 4-(4-Methoxyphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (46): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.78 (s, 3H), 7.00 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.85 (br s, 1H), 7.90 (s, 1H), 8.30 (s, 1H), 8.45 (br s, 1H), 9.05 (s, 1H); MS (DCI/NH_3) m/z 301 $(M + H)^+$. Anal. ($C_{15}H_{12}N_2O_3S$), C, H, N.

Data for *N*-Methyl-4-[4-(trifluoromethoxy)phenoxy]-thieno[2,3-*c*]pyridine-2-carboxamide (47): mp 132−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.4 Hz, 3H), 7.20 (d, J = 9.2 Hz, 2H), 7.41 (d, J = 9.2 Hz, 2H,), 8.08 (s, 1H), 8.21 (s, 1H), 8.95 (q, J = 4.4 Hz, 1H,), 9.18 (s, 1H); MS (ESI/NH_3) m/e 368 $(M + H)^+$. Anal. ($C_{16}H_{11}N_2O_3SF_3$) C, H, N.

4-(4-Acetylphenoxy)-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (48). A flask charged with iodide **9b** (500 mg, 1.2 mmol), $Pd(OAc)_2$ (27 mg, 0.12 mmol), and (o-Tol)$_3$P (110 mg, 0.36 mmol) was purged with nitrogen. Dry DMF (20 mL), tributylethoxyvinyltin (810 mL, 2.4 mmol), and triethylamine (835 mL, 6 mmol) were added via syringe. This suspension was stirred at 80 °C for 14 h, and was partitioned between ethyl acetate and 1% aqueous HCl solution. The organic phase was washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to provide ketone **48** (476 mg, 89%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H), 2.78 (d, J = 4.8 Hz, 3H), 7.15 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H), 8.03 (s, 1H), 8.36 (s, 1H), 8.98 (q, J = 4.8 Hz, 1H), 9.28 (s, 1H); MS (DCI/NH_3) m/e 327 $(M + H)^+$. Anal. ($C_{17}H_{14}N_2O_3S$) C, H, N.

Ethyl 4-{[2-(Aminocarbonyl)thieno[2,3-*c*]pyridin-4-yl]-oxy}benzoate (49). A mixture of **9a** (120 mg, 0.33 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), 1,3-bis(diphenylphosphino)-propane (20.6 mg, 0.05 mmol), and triethylamine (100 mg, 0.99 mmol) in DMF (6 mL) and ethanol (3 mL) was purged with carbon monoxide (four evacuation−fill cycles), and heated at 105 °C under a CO atmosphere (balloon) for 12 h. Ether (60 mL) was added, and the mixture was washed with brine (50 mL) and water (2 × 50 mL), dried over Na_2SO_4, and concentrated. The residual oil was purified by flash chromatography, and the product was subjected to the amidation described for **8** to give **49**: mp 242−243 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, J = 7.2 Hz, 3H), 4.30 (q, J = 7.2 Hz, 2H), 7.16 (dt, J = 9.1, 2.3 Hz, 2H), 7.82 (br s, 1H), 7.99 (dt, J = 8.8, 2.0 Hz, 2H), 8.07 (s, 1H), 8.31 (s, 1H), 8.41 (br s, 1H), 9.22 (s, 1H); MS (DCI/NH_3) m/e 343 (100, M + 1). Anal. ($C_{17}H_{14}N_2O_4S$) C, H, N.

4-(4-Aminophenoxy)thieno[2, 3-*c*]pyridine-2-carboxamide (50). 4-{4-[(*tert*-Butyloxycarbonyl)amino]phenoxy}thieno-[2,3-*c*]pyridine-2-carboxamide, which was prepared by a method analogous to the synthesis of **8**, was dissolved in trifluoroacetic acid (20 mL). This yellow solution was kept at room temperature for 1 h before TFA was removed. The residual oil was triturated with a mixture of ethyl acetate and aqueous $NaHCO_3$ solution. The formed solid was collected by filtration, washed successively with ethyl acetate, aqueous $NaHCO_3$ solution, water, methanol, and ethyl acetate, and dried to provide **50** (492 mg, 86%) as a yellow solid: mp > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.62 (br s, 2H), 6.65 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.86 (s, 1H), 8.30 (s, 1H), 8.44 (s, 1H), 9.00 (br s, 1H); MS (DCI/NH_3) m/e 286 $(M + H)^+$. Anal. ($C_{14}H_{11}N_3O_2S\cdot0.5CH_3OH$) C, H, N.

4-[4-(Acetylamino)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (51). This compound was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H), 7.10 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.82 (br s, 1H), 7.99 (s, 1H), 8.20 (s, 1H), 8.43 (br s, 1H), 9.06 (s, 1H), 9.99 (s, 1H); MS (DCI/NH_3) m/e 328 $(M+H)^+$. Anal. ($C_{16}H_{13}N_3O_3S\cdot1.0CH_3$-OH) C, H, N.

***N*-Methyl-4-(4-morpholinylphenoxy)thieno[2,3-*c*]pyridine-2-carboxamide (52).** A two-necked flask was charged with iodide **9b** (150 mg, 0.37 mmol), NaOBu^t (71 mg, 0.74 mmol), $Pd_2(dba)_3$ (14 mg, 0.014 mmol), (−)-BINAP (27 mg, 0.044 mmol), and 18-crown-6 (196 mg, 0.74 mmol), and was purged with nitrogen. Anhydrous degassed THF (10 mL) and morpholine (64 mg, 0.74 mmol) were added successively. The transparent dark red solution was heated at 60 °C for 70 h, and then quenched with brine. The mixture was extracted with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was separated by flash column chromatography on silica gel (EtOAc/hexane) and was further purified by HPLC (C-18, CH_3CN/H_2O) to provide **52** (26 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.81 (d, J = 4.5 Hz, 3H), 3.1 (m, 2H), 3.74 (m, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.92 (s, 1H), 8.20 (s, 1H), 8.98 (q, J = 4.8 Hz, 1H), 9.04 (s, 1H); MS (DCI/NH_3) m/e 370 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3O_3S$) C, H, N.

***N*-Methyl-4-[4-(4-methylpiperazin-1-yl)phenoxy]thieno-[2, 3-*c*]pyridine-2-carboxamide (53). 53** was prepared according to the procedure for **52**, substituting 4-methylpiperazine for morpholine: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.82 (d, J = 4.4 Hz, 3H), 3.18 (m, 4H), 7.00 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.92 (s, 1H), 8.20 (s, 1H), 8.98 (q, J = 4.4 Hz, 1H), 9.05 (s, 1H); MS (ESI) m/e 383 $(M + H)^+$. Anal. ($C_{20}H_{22}N_4O_2S$) C, H, N.

***N*-Methyl-4-{4-[[3-(4-methylpiperazin-1-yl)propyl]-amino]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (54). 54** was prepared according to the procedure for **52**, substituting [3-(4-methylpiperazin-1-yl)propyl]amine for morpholine: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.91 (m, 2H), 2.82 (d, J = 4.4 Hz, 3H), 2.83 (s, 3H), 3.10 (m, 6H), 3.40 (m, 6H), 6.72 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.85 (s, 1H), 8.26 (s, 1H), 8.98 (q, J = 4.4 Hz, 1H), 9.05 (s, 1H); MS (ESI) m/e 440 $(M + H)^+$. Anal. ($C_{23}H_{29}N_5O_2S$) C, H, N.

4-[4-(1*H*-Imidazol-1-yl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (55). 55 was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 310−312 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.11 (t, J = 1.1 Hz, 1H), 7.27 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.85 (br s, 1H), 8.16 (s, 1H), 8.21 (s, 1H), 8.22 (t, J = 1.0 Hz, 1H), 8.45 (br s, 1H), 9.15 (s, 1H); MS (DCI/NH_3) m/e 337 $(M + H)^+$. Anal. ($C_{17}H_{12}N_4O_2S\cdot0.50H_2O$) C, H, N.

***N*-Methyl-4-[4-(1*H*-Imidazol-1-yl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (56)**. **56** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 253−254 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.81 (d, J = 5.0 Hz, 3H), 7.11 (s, 1H), 7.26 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.72 (s, 1H), 8.12 (s, 1H), 8.19 (s, 1H), 8.21 (s, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 118.2, 119.0, 119.0, 122.4, 129.8, 132.9, 132.9, 135.6, 137.3, 137.9, 141.2, 146.1, 147.4, 155.1, 160.9; MS (APCI) m/e 351 $(M + H)^+$, 385 $(M + Cl)^-$. Anal. ($C_{18}H_{14}N_4O_2S$) C, H, N.

***N*-Methyl-4-[4-(1*H*-pyrazol-1-yl)phenoxy]thieno[2,3-*c*]-pyridine-2-carboxamide (57). 57** was prepared from dichlo-

ropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 192−194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.4 Hz, 3H), 6.55 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H), 7.90 (d, J = 9.2 Hz, 2H), 8.12 (s, 1H), 8.20 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 9.00 (q, J = 4.4 Hz, 1H), 9.18 (s, 1H); MS (DCI/NH_3) m/e 351 $(M + H)^+$. Anal. ($C_{18}H_{14}N_4O_2S \cdot 0.25H_2O$) C, H, N.

***N*-Methyl-4-[4-(1*H*-1,2,4-triazol-1-yl)phenoxy]thieno-[2,3-*c*]pyridine-2-carboxamide (58)**. **58** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 214−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.6 Hz, 3H), 7.30 (d, J = 8.8 Hz, 2H), 7.54 (br s, 1H), 7.90 (d, J = 9.0 Hz, 2H), 8.11 (s, 1H), 8.24 (d, J = 2.6 Hz, 1H), 9.00 (q, J = 4.2 Hz, 1H), 9.28 (s, 1H); MS (DCI/NH_3) m/e 352 $(M + H)^+$.

***N*-Methyl-4-[4-(1-methyl-1*H*-imidazol-5-yl)phenoxy]-thieno[2,3-*c*]pyridine-2-carboxamide (59). 59** was prepared according to the procedure for **62,** substituting 1-methyl-5-(tributylstannyl)imidazole, which was prepared according to the procedure of Gaare,[28] for 2-(tributylstannyl)thiophene: mp 256−258 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 2.1 Hz, 3H), 3.67 (s, 3H), 7.03 (s, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.69 (s, 1H), 8.12 (s, 1H), 8.22 (s, 1H), 9.00 (q, J = 2.1 Hz, 1H), 9.16 (s, 1H); MS (ESI/NH_3) m/e 365 $(M + H)^+$. Anal. ($C_{19}H_{16}N_4O_2S$) C, H, N.

***N*-Methyl-4-{4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (60).** A suspension of **12c** (200 mg, 0.58 mmol) in pyridine (8 mL) was treated with trifluoroacetic anhydride (178 mg, 0.85 mmol) at room temperature for 1 h. The resultant yellow solution was heated at 120 °C for 18 h, and was then concentrated. The residue was separated by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to afford **60** (169 mg, 69%): mp 174−176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78 (d, J = 4.4 Hz, 3H), 7.26 (d, J = 8.8 Hz, 2H), 8.03 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.38 (s, 2H), 8.96 (q, J = 4.4 Hz, 1H), 9.25 (s, 1H); MS (ESI/NH_3) m/e 421 $(M + H)^+$. Anal. ($C_{18}H_{11}N_4O_3SF_3$) C, H, N.

4-([1,1′-Biphenyl]-4-yloxy)-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (61). 61 was prepared according to the procedure for **62,** substituting tributylphenyltin for 2-(tributylstannyl)thiophene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.5 Hz, 3H), 7.19 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.3 Hz, 2H), 7.66 (d, J = 7.3 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 8.15 (s, 1H), 8.23 (s, 1H), 9.00 (q, J = 4.4 Hz, 1H), 9.19 (s, 1H); MS (ESI/NH_3) m/e 361 $(M + H)^+$. Anal. ($C_{21}H_{16}N_2O_2S$) C, H, N.

***N*-Methyl-4-[4-(2-thienyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (62).** A two-necked flask was charged with iodide **9b** (200 mg, 0.48 mmol), $Pd(OAc)_2$ (11 mg, 0.048 mmol), and tri-*o*-tolylphosphine (44 mg, 0.14 mmol), and was purged with nitrogen. Dry degassed DMF (10 mL), 2-(tributylstannyl)-thiophene (305 μL, 0.96 mmol), and triethylamine (334 μL, 2.4 mmol) were added. This suspension was stirred at 80 °C for 15 h and was partitioned between ethyl acetate and brine. The organic phase was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was separated by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to afford **62** (212 mg, 90%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.4 Hz, 3H), 7.13 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 8.15 (s, 1H), 8.24 (s, 1H), 9.02 (q, J = 4.4 Hz, 1H), 9.22 (s, 1H); MS (ESI/NH_3) m/e 367 $(M + H)^+$. Anal. ($C_{19}H_{14}N_2O_2S_2$) C, H, N.

***N*-Methyl-4-[4-(2-furyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (63)**. Compound **63** was prepared according to the procedure for **62,** substituting 2-(tributylstannyl)furan for 2-(tributylstannyl)thiophene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.82 (d, J = 4.4 Hz, 3H), 6.60 (m, 1H), 6.95 (d, J = 4.0 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 7.77 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 8.25 (s, 1H), 9.00 (q, J = 4.4 Hz, 1H), 9.22 (s, 1H); MS (ESI/NH_3) m/e 351 $(M + H)^+$. Anal. ($C_{19}H_{14}N_2O_3S \cdot 0.85$TFA) C, H, N.

4-{4-[3-Hydroxy-3-[4-[[2-[(methylamino)carbonyl]-thieno[2,3-*c*]pyridin-4-yl]oxy]phenyl]butanoyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (64). A solution of ketone **48** (200 mg, 0.45 mmol) in THF (5 mL) was treated with methylmagnesium bromide (3 M solution in ether, 0.18 mL, 0.55 mmol) at −50 °C for 30 min, and slowly warmed to room temperature over 10 min. Aqueous NH_4Cl solution was added, and the mixture was extracted with ether. The combined organic phases were washed with brine and water, dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 5% MeOH/EtOAc to provide **64** (60 mg, 40%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.58 (s, 3H), 2.77 (d, J = 4.8 Hz, 3H), 2.80 (d, J = 4.8 Hz, 3H,), 3.35 (d, J = 13.0 Hz, 1H,), 3.49 (d, J = 13.0 Hz, 1H), 5.27 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.99 (s, 2H), 8.13 (s, 1H), 8.30 (s, 1H), 8.94 (m, 2H), 9.08 (s, 1H), 9.21 (s, 1H); MS (ESI/NH_3) m/e 653 $(M + H)^+$. Anal. ($C_{34}H_{28}N_4O_6S_2 \cdot CH_3OH$) C, H, N.

4-{4-[[Cyclohexyl[(cyclohexylamino)carbonyl]amino]-carbonyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (65). A solution of DCC (74 mg, 0.36 mmol) and **10c** (100 mg, 0.3 mmol) in a mixture of CH_2Cl_2 (5 mL) and DMF (1 mL) was treated with 4-(2-aminoethyl)morpholine (48 mg, 0.36 mmol) at room temperature for 60 h. The crude reaction mixture was directly separated by flash chromatography. The product was subjected to amidation as described for **8** to give **65**: IR (KBr, cm^{-1}) 3450 (w), 3350 (w), 3200 (m), 1715 (s), 1680 (s); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00−1.28 (m, 10H), 1.50−1.75 (m, 10H), 3.30 (m, 2H), 5.55 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.82 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H), 8.31 (s, 1H), 8.41 (s, 1H), 9.21 (s, 1H); MS (DCI/NH_3) m/e 521 $(M + H)^+$. Anal. ($C_{28}H_{32}N_4O_4S \cdot 2CH_3OH$) C, H, N.

General Method for the Synthesis of 66−73. A solution of **10d** (1.76 g, 4.2 mmol) in chloroform (50 mL) was treated with trifluoroacetic acid (10 mL) at room temperature for 4 h, and was then poured into ice-cold aqueous $NaHCO_3$. The formed white solid was collected by filtration, washed with water, MeOH, and CH_2Cl_2, and dried to afford methyl 4-{4-[(*E*)-propenoic acid-1-yl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxylate (1.38 g, 100%).

A solution of this acid (0.5 mmol) in DMF (7 mL) was treated with the appropriate amine (1 mmol), EDC (1 mmol), HOBt·H_2O (1 mmol), and triethylamine (1 mmol) at room temperature for 18 h. After being diluted with EtOAc, the reaction mixture was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography, and the product was subjected to amidation as described for **8** (Method A) to provide compounds **66**−**73**.

Data for 4-{4-[(*E*)-3-(4-Morpholinyl)-3-oxo-1-propenyl]-phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (66): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.59 (m, 6H), 3.70 (m, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 15.5 Hz, 1H), 7.52 (d, J = 15.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.86 (s, 1H), 8.16 (s, 1H), 8.18 (s, 1H), 8.45 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) m/e 410 $(M + H)^+$. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N.

Data for 4-{4-[(*E*)-3-[[2-(4-Morpholinyl)ethyl]amino]-3-oxo-1-propenyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (67): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.44 (m, 4H), 3.30 (m, 4H), 3.59 (t, J = 4.8 Hz, 4H), 6.60 (d, J = 15.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.87 (s, 1H), 8.06 (t, J = 4.8 Hz, 1H), 8.16 (s, 1H), 8.21 (s, 1H), 8.45 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) m/e 453 $(M + H)^+$. Anal. ($C_{23}H_{24}N_4O_4S$) C, H, N.

Data for *N*-Methyl-4-{4-[(*E*)-3-[[2-(4-morpholinyl)ethyl]-amino]-3-oxo-1-propenyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (68): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (m, 4H), 2.79 (d, J = 4.4 Hz, 3H), 3.59 (m, 8H), 6.58 (d, J = 15.8 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 8.05 (s, 1H), 8.23 (s, 1H), 8.95 (q, J = 4.4 Hz, 1H), 9.17 (s, 1H); MS (DCI/NH_3) m/e 467 $(M + H)^+$. Anal. ($C_{24}H_{26}N_4O_4S$) C, H, N.

Data for 4-{4-[(*E*)-3-[(2,3-Dihydroxypropyl)amino]-3-oxo-1-propenyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (69): mp 185−187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.10 (m, 1H), 3.30 (m, 2H), 3.54 (m, 1H), 4.60 (t, J = 5.9 Hz, 1H), 4.84 (d, J = 4.8 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.13

(d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.86 (s, 1H), 8.08 (t, J = 5.5 Hz, 1H), 8.16 (s, 1H), 8.21 (s, 1H), 8.45 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/e* 414 $(M + H)^+$. Anal. ($C_{20}H_{19}N_3O_5S$) C, H, N.

Data for 4-{4-[(*E*)-3-[(2,3-Dihydroxypropyl)amino]-3-oxo-1-propenyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (70): mp 225−226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.8 Hz, 3H), 3.10 (m, 1H), 3.30 (m, 2H), 3.54 (m, 1H), 4.60 (t, J = 5.5 Hz, 1H), 4.84 (d, J = 4.8 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H), 8.08 (t, J = 5.5 Hz, 1H), 8.23 (s, 1H), 8.97 (q, J = 4.8 Hz, 1H), 9.18 (s, 1H); MS (DCI/NH_3) *m/e* 428 $(M + H)^+$. Anal. ($C_{21}H_{21}N_3O_5S$) C, H, N.

Data for 4-{4-[(*E*)-3-[[2-[Bis(2-hydroxyethyl)amino]-ethyl]amino]-3-oxo-1-propenyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (71): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56 (m, 4H), 3.21 (m, 2H), 3.41 (m, 4H), 4.37 (t, J = 5.6 Hz, 2H), 6.56 (d, J = 15.4 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.4 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.86 (s, 1H), 8.00 (t, J = 5.5 Hz, 1H), 8.15 (s, 1H), 8.21 (s, 1H), 8.45 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/e* 471 $(M + H)^+$. Anal. ($C_{23}H_{26}N_4O_5S \cdot CH_3OH$) C, H, N.

Data for 4-{4-[(*E*)-3-[[2-[Bis(2-Hydroxyethyl)amino]-ethyl]amino]-3-oxo-1-propenyl]phenoxy}-*N*-methylthieno-[2,3-*c*]pyridine-2-carboxamide (72): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.8 Hz 3H), 3.34 (m, 6H), 3.58 (q, J = 6.1 Hz, 2H), 3.77 (t, J = 5.1 Hz, 4H), 6.55 (d, J = 15.6 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 15.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H), 8.24 (s, 1H), 8.43 (t, J = 4.8 Hz, 1H), 8.97 (q, J = 4.8 Hz, 1H), 9.20 (s, 1H); MS (DCI/NH_3) *m/e* 485 $(M + H)^+$. Anal. ($C_{24}H_{28}N_4O_5S$) C, H, N.

Data for 4-{4-[(*E*)-3-[[2-(1*H*-Imidazol-4-yl)ethyl]amino]-3-oxo-1-propenyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (73): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.5 Hz, 3H), 2.85 (t, J = 6.6 Hz, 2H), 3.49 (q, J = 6.0 Hz, 2H), 6.53 (d, J = 15.8 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 7.47 (s, 1H), 7.61 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H), 8.24 (s, 1H), 8.27 (t, J = 5.5 Hz, 1H), 8.97 (q, J = 4.8 Hz, 1H), 9.01 (s, 1H), 9.21 (s, 1H); MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{23}H_{21}N_5O_3S$) C, H, N.

General Method for the Synthesis of Compounds 74−78. A solution of **10c** (0.5 mmol) in DMF (10 mL) was treated with the appropriate amine (1 mmol), EDC (1 mmol), HOBt·H_2O (1 mmol), and triethylamine (1 mmol) at room temperature for 18 h. After being diluted with EtOAc, the reaction mixture was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography, and the product was subjected to amidation as described for **8** to give the designated compound.

Data for 4-[4-(4-Morpholinylcarbonyl)phenoxy]thieno-[2,3-*c*]pyridine-2-carboxamide (74): mp > 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.50 (m, 4H), 3.60 (m, 4H), 7.14 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.86 (s, 1H), 8.15 (s, 1H), 8.22 (s, 1H), 8.45 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/e* 401 $(M + NH_4)^+$. Anal. ($C_{19}H_{17}N_3O_4S$) C, H, N.

Data for *N*-Methyl-4-[4-(4-morpholinylcarbonyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (75): mp 173−175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.4 Hz, 3H), 3.50 (m, 4H), 3.60 (m, 4H), 7.12 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H), 8.24 (s, 1H), 8.96 (q, J = 4.4 Hz, 1H), 9.18 (s, 1H); MS (DCI/NH_3) *m/e* 415 $(M + NH_4)^+$. Anal. ($C_{20}H_{19}N_3O_4S$) C, H, N.

Data for 4-{4-[[[2-(4-Morpholinyl)ethyl]amino]carbonyl]-phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (76): mp 214−216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (t, J = 4.8 Hz, 4H), 3.37 (q, J = 6.1 Hz, 2H), 3.56 (t, J = 4.8 Hz, 4H), 7.14 (d, J = 8.8 Hz, 2H), 7.84 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 8.11 (s, 1H), 8.22 (s, 1H), 8.39 (t, J = 6.0 Hz, 1H), 8.43 (s, 1H), 9.17 (s, 1H); MS (DCI/NH_3) *m/e* 427 $(M + H)^+$. Anal. ($C_{21}H_{22}N_4O_4S$) C, H, N.

Data for *N*-Methyl-4-{4-[[[2-(4-morpholinyl)ethyl]amino]-carbonyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (77): mp 226−228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (m, 4H), 2.78 (d, J = 4.4 Hz, 3H), 3.36 (q, J = 6.1 Hz, 2H), 3.56 (t, J = 4.8 Hz, 4H), 7.12 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 8.03 (s, 1H), 8.26 (s, 1H), 8.41 (t, J = 6.0 Hz, 1H), 8.95 (q, J = 4.4 Hz, 1H), 9.20 (s, 1H); MS (DCI/NH_3) *m/e* 441 $(M + H)^+$. Anal. ($C_{22}H_{24}N_4O_4S$) C, H, N.

Data for 4-{4-[[(2,3-Dihydroxypropyl)amino]carbonyl]-phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (78): mp 230−232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m, 1H), 3.40 (m, 1H), 3.62 (m, 1H), 4.58 (t, J = 5.9 Hz, 1H), 4.82 (d, J = 4.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.82 (br s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.10 (s, 1H), 8.22 (s, 1H), 8.40 (t, J = 5.5 Hz, 1H), 8.42 (s, 1H), 9.20 (s, 1H); MS (DCI/NH_3) *m/e* 405 (M + NH_4)$^+$. Anal. ($C_{18}H_{17}N_3O_5S$) C, H, N.

4-{4-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]phenoxy}-thieno[2,3-*c*]pyridine-2-carboxamide (79). Compound **79** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 95−96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (m, 4H), 1.69 (m, 2H), 3.49 (m, 1H), 3.80 (m, 1H), 4.44 (d, J = 12.1 Hz, 1H), 4.67 (d, J = 12.1 Hz, 1H), 4.70 (m, 1H), 7.10 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.87 (s, 1H), 8.08 (s, 1H), 8.20 (s, 1H), 8.46 (s, 1H), 9.12 (s, 1H); MS (DCI/NH_3) *m/e* 385(M + H)$^+$. Anal. ($C_{20}H_{20}N_2O_4S \cdot CH_3OH$) C, H, N.

4-[4-(Methoxymethyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (80). Compound **80** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 168−168.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (s, 3H), 4.41 (s, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.86 (s, 1H), 8.08 (s, 1H), 8.19 (s, 1H), 8.45 (br s, 1H), 9.12 (s, 1H); MS (DCI/NH_3) *m/z* 315 $(M + H)^+$. Anal. ($C_{16}H_{14}N_2O_3S$) C, H, N.

4-[4-(Methoxymethyl)phenoxy]-*N*-methylthieno[2,3-*c*]-pyridine-2-carboxamide (81). Compound **81** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8**: mp 163−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79 (d, J = 4.4 Hz, 3H), 3.29 (s, 3H), 4.40 (s, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 8.09 (s, 1H), 8.12 (s, 1H), 8.94 (q, J = 4.4 Hz, 1H), 9.12 (s, 1H); MS (DCI/NH_3) *m/e* 329 $(M + H)^+$. Anal. ($C_{17}H_{16}N_2O_3S$) C, H, N.

4-[4-(Hydroxymethyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (82). A solution of methyl 4-{4-[(trityloxy)-methyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxylate (5.05 g, 9 mmol), which was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **6**, in a mixture of chloroform (20 mL) and methanol (8 mL) was treated with trifluoroacetic acid (10 mL) at 0 °C for 6 h. This solution was then poured into a mixture of ice and saturated aqueous $NaHCO_3$. The mixture was extracted with methylene chloride (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to give methyl 4-[4-(hydroxymethyl)phenoxy]thieno-[2,3-*c*]pyridine-2-carboxylate (2.11 g, 74%). This methyl ester was treated with methanolic ammonia as described for **8** (method A) to give **82**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.50 (d, J = 5.8 Hz, 2H), 5.19 (t, = 5.8 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.82 (br s, 1H), 8.03 (s, 1H), 8.20 (s, 1H), 8.43 (br s, 1H), 9.09 (s, 1H); MS (DCI/NH_3) *m/e* 301 $(M + H)^+$. Anal. ($C_{15}H_{12}N_2O_3S$) C, H, N.

4-[4-(Hydroxymethyl)phenoxy]-*N*-methylthieno[2,3-*c*]-pyridine-2-carboxamide (83). Compound **83** was prepared according to the procedure for **82**, substituting methanolic methylamine for methanolic ammonia: mp 195−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (d, J = 4.5 Hz, 3H), 4.49 (d, J = 4.5 Hz, 2H), 5.19 (t, J = 4.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H), 8.11 (s, 1H), 8.94 (q, J = 4.5 Hz, 1H), 9.10 (s, 1H); MS (DCI/NH_3) *m/e* 315 $(M + H)^+$. Anal. ($C_{16}H_{14}N_2O_3S \cdot 0.75CH_3OH$) C, H, N.

4-[4-(1,2-Dihydroxyethyl)phenoxy]thieno[2,3-*c*]pyridine-2-carboxamide (84). A solution of **34** (35 mg, 0.118 mmol) in pyridine (5 mL) was treated with OsO_4 (90 mg, 0.354 mmol) at room temperature for 5 h. Aqueous $NaHSO_3$ (10%) (1 mL) was added, and the mixture was stirred for 2 h. After being diluted with ethyl acetate, the reaction mixture was washed with 1% aqueous HCl and brine, dried (Na_2SO_4), and

concentrated. The residue was purified by flash chromatography on silica gel to afford **84**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.44 (t, J = 5.9 Hz, 2H), 4.55 (q, J = 6.0 Hz, 1H), 4.73 (t, J = 6.0 Hz, 1H), 5.27 (d, J = 4.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.85 (br s, 1H), 8.03 (s, 1H), 8.21 (s, 1H), 8.47 (br s, 1H), 9.10 (s, 1H); MS (DCI/NH_3) m/z 331 $(M + H)^+$. Anal. ($C_{16}H_{14}N_2O_4S \cdot 0.25CH_3OH$) C, H, N.

4-{4-[(2-Methoxyethoxy)methyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (85). Compound **85** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8** (method A): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.60 (m, 2H), 3.65 (m, 2H), 4.56 (s, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.80 (s, 1H), 8.13 (s, 1H), 8.94 (s, 1H); MS (DCI/NH_3) m/e 359 $(M + H)^+$. Anal. ($C_{18}H_{18}N_2O_4S$) C, H, N.

4-{4-[(2-Methoxyethoxy)methyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (86). Compound **86** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8** (method A): mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (d, J = 5.1 Hz, 3H), 3.40 (s, 3H), 3.60 (m, 2H), 3.65 (m, 2H), 4.54 (s, 2H), 6.51 (q, J = 5.1 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.73 (s, 1H), 8.14 (s, 1H), 8.94 (s, 1H); MS (DCI/NH_3) m/e 373 $(M + H)^+$. Anal. ($C_{19}H_{20}N_2O_4S$) C, H, N.

4-{4-[[2-(2-Methoxyethoxy)ethoxy]methyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxamide (87). Compound **87** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8** (method A): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.57 (m, 2H), 3.63−3.70 (m, 6H), 4.55 (s, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.71 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); MS (DCI/NH_3) m/e 403 $(M + H)^+$. Anal. ($C_{20}H_{22}N_2O_5S$) C, H, N.

4-{4-[[2-(2-Methoxyethoxy)ethoxy]methyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (88). Compound **88** was prepared from dichloropyridinecarboxaldehyde **4** as described in the general synthesis of **8** (method A): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (d, J = 4.8 Hz, 3H), 3.38 (s, 3H), 3.57 (m, 2H), 3.63−3.70 (m, 6H), 4.54 (s, 2H), 6.45 (m, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.72 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H); MS (DCI/NH_3) m/e 417 $(M + H)^+$. Anal. ($C_{21}H_{24}N_2O_5S$) C, H, N.

4-{4-[1-(Hydroxymethyl)cyclopropyl]phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (93). To a suspension of NaH (60% in mineral oil, 392 mg, 9.8 mmol) in DMF (10 mL) was slowly added neat ethanethiol (610 mg, 9.8 mmol) at room temperature. The reaction mixture was stirred for 10 min to form a transparent solution. 4-[1-(Hydroxymethyl)-cyclopropyl]anisole (500 mg, 2.8 mmol) was added, and the mixture was heated at 145 °C for 4 h. Ether was added, and the reaction mixture was washed with 2% HCl in brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel with 50% EtOAc/hexane to afford 4-[1-(hydroxymethyl)cyclopropyl]phenol (373 mg, 81%).

A solution of this phenol (1.0 g, 6 mmol) in pyridine (7 mL) was treated with triphenylmethyl chloride (1.87 g, 6.7 mmol) at room temperature for 18 h. Ether was added, and the reaction mixture was washed with 1% aqueous HCl and water and dried ($MgSO_4$). The residue was purified by flash chromatography to give 4-{1-[(triphenylmethoxy)methyl]cyclopropyl}phenol, which was subjected to the cyclization reaction as described for **6** to provide methyl 4-{4-[1-[(triphenylmethoxy)-methyl]cyclopropyl]phenoxy}thieno[2,3-*c*]pyridine-2-carboxylate. A solution of this trityl methyl ester (230 mg, 0.38 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (5 mL) was treated with trifluoroacetic acid (1 mL) at 0 °C for 1 h, and at room temperature for another hour. The reaction mixture was poured into aqueous $NaHCO_3$ solution, and was extracted with methylene chloride. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography, and the product was subjected to the amidation as described for **8** to give **93**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.72 (m, 2H), 0.82 (m, 2H), 2.80 (d, J = 4.7 Hz, 3H), 3.51 (d, J = 5.8 Hz, 2H), 4.66 (t, J = 5.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H), 8.13 (s, 1H), 8.96 (q, J = 4.7 Hz, 1H), 9.10 (s, 1H); MS (ESI/NH_3) m/e 355 $(M + H)^+$. Anal. ($C_{19}H_{18}N_2O_3S$) C, H, N.

4-{4-[1-[[2-(2-Ethoxyethoxy)ethoxy]methyl]cyclopropyl]-phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (94). A solution of 4-[1-(hydroxymethyl)cyclopropyl]anisole (1.0 g, 5.6 mmol) in THF (15 mL) was treated with NaH (60% in mineral oil, 312 mg, 7.8 mmol) and 15-crown-5 (1.33 mL, 6.7 mmol) at room temperature for 15 min. 2-(2-Ethoxyethoxy)-ethyl tosylate (1.93 g, 6.7 mmol, prepared according to the method of Amansa et al.[29]) was then added. The brown slurry was stirred at room temperature for 5 h and then poured into brine. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to afford 4-{1-[[2-(2-ethoxyethoxy)ethoxy]methyl]cyclopropyl}-anisole (1.58 g, 95%).

A solution of this anisole (1.5 g, 5.1 mmol) in DMF (15 mL) was treated with sodium thiomethoxide (1.25 g, 17.8 mmol) at 145 °C for 5 h. Methylene chloride (100 mL) was added, and the mixture was washed with 2% HCl in brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel with 35% EtOAc/hexane to provide the corresponding phenol (1.33 g, 93%). This phenol was subjected to cyclization and amidation as described for **6** and **8** to give **94**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (m, 2H), 0.87 (m, 2H), 1.06 (t, J = 6.7 Hz, 3H), 2.82 (d, J = 4.4 Hz, 3H), 3.37 (t, J = 6.7 Hz, 2H), 3.39−3.55 (m, 10H), 7.07 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 8.13 (s, 1H), 8.26 (s, 1H), 9.10 (q, J = 4.4 Hz, 1H), 9.28 (s, 1H); MS (ESI/NH_3) m/e 471$(M + H)^+$. Anal. ($C_{25}H_{30}N_4O_5S$) C, H, N.

4-{4-[2-[2-(2-Ethoxyethoxy)ethoxy]-1,1-difluoroethyl]-phenoxy}-*N*-methylthieno[2,3-*c*]pyridine-2-carboxamide (95). A solution of **10f** (40 mg, 0.11 mmol) in THF (3 mL) was treated with NaH (60% in mineral oil, 7 mg, 0.16 mmol) and 15-crown-5 (35 mg, 0.16 mmol) at room temperature for 15 min. 2-(2-Ethoxyethoxy)ethyl tosylate (46 mg, 0.16 mmol) was then added. The reaction mixture was stirred at room temperature for 15 h, and was then directly purified by HPLC (C-18, CH_3CN/H_2O containing 0.1% TFA) to afford **95** (46 mg, 81%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.16 (t, J = 7.1 Hz 3H,), 2.97 (s, 3H), 3.49 (q, J = 7.1 Hz, 2H), 3.57 (m, 6H), 3.70 (m, 2H), 4.01 (t, J = 12.7 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 8.22 (s, 1H), 8.33 (s, 1H), 9.46 (s, 1H); MS (ESI/NH_3) m/e 481 $(M + H)^+$. Anal. ($C_{23}H_{26}F_2N_2O_5S$) C, H, N.

Biology. 1. Cell ELISA Assay. Primary HUVECs were plated in 96-well plates at 5×10^4 cells/mL in EBM/2% FBS/human epidermal growth factor/bovine brain extract/gentamicin (Clonetics/BioWhitaker). The following day test compounds were added and the plates incubated for 24 h at 37 °C. TNFα (Gibco/BRL) then was added to a final concentration of 5 ng/mL, and the plates were incubated for an additional 6 h at 37 °C. The plates were washed once with D-PBS (Gibco/BRL), and primary antibody (Becton Dickinson) was added in D-PBS/2% BSA (Sigma)/0.01% NaN_3. The antibodies used were mouse monoclonal anti-ELAM-1, anti-ICAM-1, and anti-VCAM-1. The plates were stored overnight at 4 °C and then washed three times with D-PBS. Secondary antibody, HRP-conjugated donkey anti-mouse IgG (Jackson Labs) in D-PBS/2%BSA, was added, and the plates were incubated for 1−2 h at room temperature and then washed three times with D-PBS. OPD solution (Abbott) was added to the wells, the plates were developed for 15−20 min and neutralized with 1 N sulfuric acid, and the absorbance was read at 490 nm.

For assays using alternative inducing agents, IL-1β, PMA, or LPS was substituted for TNFα in the above protocol.

2. Toxicity Assays. Primary HUVECs were plated and treated with test compounds and TNFα as described for the ELISA assays. Approximately 24 h after compound addition, Promega MTS reagent was added to the culture wells. After the cultures were incubated for an additional 2 h at 37 °C, the absorbance was read at 490 nm.

3. Flow Adhesion Assay. The apparatus for determining the ability of the test compounds to inhibit the rolling adhesion

of HL60 cells on a monolayer of human umbilical vein endothelial cells was performed with a Glycotech flow cell according to the method of Patten.[30]

Pharmacokinetic Analysis. The pharmacokinetic behavior of the compounds was evaluated in male Sprague−Dawley rats. Briefly, the test compound was prepared as a 10 mg/mL solution in an ethanol/propylene glycol.D5W (20:30:50, by volume) vehicle. The corresponding equivalent of base or acid was added to neutralize the tested compound. Groups of rats (n = 4/group) received either a 5 mg/kg intravenous dose administered as a slow bolus in the jugular vein or a 5 mg/kg oral dose administered by gavage. Heparinized blood samples (∼0.4 mL/sample) were obtained from a tail vein of each rat 0.1 (iv only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after dosing. The samples were analyzed by reversed-phase HPLC following liquid−liquid extraction from the plasma.

In Vitro Metabolism of 86. Compound **86** was incubated with commercially obtained rat hepatocytes (Cedra Corp.) for 24 h at a substrate concentration of approximately 200 μM. Several incubation reactions were pooled and were separated by semipreparative HPLC (C18 column with 20 mM NH_4OAc/ACN as mobile phase). The eluents from five distinct regions of the trace were collected, and analyzed by LC/MS and flow injection analysis/MS. The fraction (no. 4) that contained drug-related metabolites was further analyzed by LC/MS/MS and high-resolution MS. The ions examined were *m/z* 309, *329*, 335, 353, *359*, *360*, 367, *389*, 395, and *453*. The ions in italics correspond to the masses of predicted metabolites of **86**. NB-positive-mode ionization was used, so all peaks correspond to $[M + H]^+$.

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